SEALED DOCUMENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: Stamm et al

Application No. 10/288,425 Group Art Unit: 1615

Filed: November 6, 2002 Examiner: H. Sheikh

For: **FENOFIBRATE PHARMACEUTICAL COMPOSITION HAVING HIGH BIOAVAILABILITY AND METHOD FOR PREPARING IT**

Attorney Docket No: 107664.115US6

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Declaration under 37 C.F.R. § 1.132

I, Philippe Réginault, declare as follows.

1. I am a 1973 graduate of the INA in France.

2. I have been employed by Laboratoires Fournier, the assignee of the above-identified application, since 1981. I successively held the following positions within Laboratoires Fournier:

- 1981-1985: Head of section "Research of Natural Products" (Selection of plants for extraction and search for biologically active substances).
- 1985-1988: Vice-manager of Bio formulation.
- 1988-2002: Director of Pharmaceutical Development (in charge of Formulation, Scale up, Analytical Development, CMC section and Clinical Supplies).
- 2002-Present: Director of Pharmaceutical Technologies Evaluation.

3. I have been named in the following publications, including patents (original French titles): process for preparing a therapeutically useful extract from Brackenridgea zanguebarica, extract and such a medicine (EP 0126691); self-adhesive device for transdermal administration of an active agent (U.S. Patent Nos. 4,842,864 and 4,837,025); treatment of impotence (US Patent No. 5,451,609); treatment of acute urinary retention (US Patent No. 5,561,154); Update in theophylline therapy : monodisperse spherical microbeads permitting user's self dosage adjustment; B. Curtet; M. Lamoise; P. Réginault; E. Teillaud; Poster 15th International Symposium on Controlled Release of Biomaterials. 1988; Cellules à flux

continu: exemples d'application aux microsphères, à différents pH; B. Curtet; M. Lamoise; P. Réginault; E. Teillaud; S.T.P. Pharma (1990), 6(9), 673-7; Micronized fenofibrate; J.P. Guichard; A. Munoz; P. Réginault; Atherosclerosis (1994), 110, S45-S48; Assessing the particle size of a broadly dispersed powder by complementary techniques; C. Andrès; P. Bracconi; P. Réginault; P. Blouquin; M.H. Rochat; Y. Pourcelot; International Journal of Pharmaceutics 167, (1998), 129-138.

4. I am a co-inventor of U.S. Patent No. 4,895,726 (the Curtet reference), which has been cited by the U.S. Patent Office to reject the claims in the above-identified application.

5. I have read and understood PCT/IB98/00065, and the U.S. Application Nos. 09/899,026 and 10/288,425 (i.e., the above-identified application).

6. I have read and understood U.S. Patent No. 4,800,079 (the Boyer reference).

7. To the best of my knowledge, the product Lipanthyl® 250 (manufactured by Ethypharm and marketed by Laboratoires Fournier) is manufactured in accordance with the teachings in U.S. Patent No. 4,800,079 (the Boyer reference). Lipanthyl® 250 contains 250 mg of fenofibrate is manufactured as a capsule containing microgranules. In the following Tables and Figures, Lipanthyl® 250 is identified as batch 70825.

8. To the best of my knowledge, the product Lipanthyl® Supra (manufactured and marketed by Laboratoires Fournier) is manufactured in accordance with the teachings in PCT/IB98/00065 and the above-identified application. Lipanthyl® Supra contains 160 mg of fenofibrate and is manufactured as a tablet. In the following Tables and Figures, Lipanthyl® Supra is identified as batch 72197.

9. I supervised dissolution tests where the dissolution was determined using a paddle apparatus, USP type 2. The paddle speed was 75 rpm. The dissolution medium was 1.00 L of 0.025 M aqueous sodium laurylsulfate at 37 ± 0.5°C.

10. For the test, six units (i.e., tablets or capsules) were tested. In order to exclude the lag time due to the capsule opening for Lipanthyl® 250, the microgranules contained in each capsule were used as the test samples. The dissolution medium was sampled at 5, 10, 20, 30 and 60 minutes. The fenofibrate concentration in the dissolution medium samples was determined by ultra-violet spectrophotometry at the maximum absorbance wavelength of fenofibrate.

11. The results are given in the following Tables 1 and 2, where the amounts of fenofibrate dissolved in the medium are expressed either as % of the label strength or as mg fenofibrate dissolved. Figures 1 and 2 below are a graphical representation of the numerical results found in Tables 1 and 2, respectively.

Table 1: Dissolution of Lipanthyl® Supra Corresponding to Claims in US Application No. 10/288,425

Time (min)	Unit dose 1	2	3	4	5	6	Mean	SD	RSD %
% dissolved									
5	33.0	31.9	26.5	18.6	26.1	24.5	26.8	5.2	19.6
10	65.2	63.2	61.5	51.8	61.8	59.5	60.5	4.7	7.7
20	82.6	82.3	83.9	83.8	83.4	81.7	83.0	0.9	1.1
30	89.4	89.6	89.7	92.5	89.6	88.3	89.8	1.4	1.5
60	94.8	95.2	96.2	99.4	94.7	94.2	95.7	1.9	2.0
mg dissolved									
5	52.8	51.1	42.4	29.7	41.8	39.2	43	8.40	19.6
10	104.3	101.1	98.4	82.9	98.9	95.2	97	7.46	7.7
20	132.2	131.7	134.3	134.1	133.4	130.8	133	1.40	1.1
30	143.0	143.4	143.6	147.9	143.3	141.4	144	2.20	1.5
60	151.7	152.3	154.0	159.0	151.6	150.7	153	3.05	2.0

Table 2: Dissolution of Lipanthyl® 250 Corresponding to U.S. Patent No. 4,800,079 to Boyer

Time (min)	Unit dose 1	2	3	4	5	6	Mean	SD	RSD %
% dissolved									
5	0.3	0.4	0.3	0.3	0.3	0.3	0.4	0.0	9.8
10	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.0	0.0
20	1.2	1.2	1.2	1.2	1.2	1.3	1.2	0.0	2.9
30	1.8	1.8	1.9	1.9	1.9	2.0	1.9	0.1	3.4
60	3.9	4.0	4.0	4.0	3.9	4.6	4.0	0.3	6.5
mg dissolved									
5	0.9	1.1	0.9	0.9	0.9	0.9	0.9	0.1	9.8
10	1.5	1.5	1.5	1.5	1.5	1.5	1.5	0.0	0.0
20	3.0	3.0	3.0	3.0	3.0	3.2	3.1	0.1	2.9
30	4.5	4.5	4.7	4.7	4.7	5.0	4.7	0.2	3.4
60	9.7	9.9	9.9	9.9	9.7	11.4	10.1	0.7	6.5

Figure 1

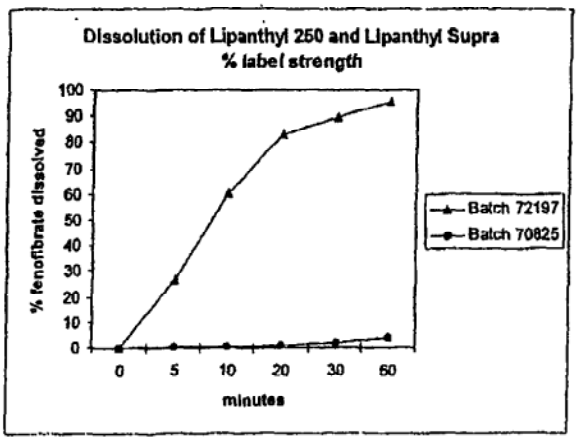
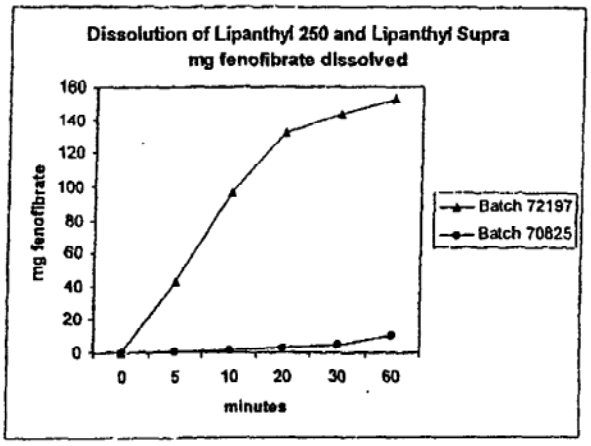


Figure 2



12. The results shown above clearly demonstrate that Lipanthyl® 250 (*i.e.*, U.S. Patent No. 4,800,079 to Boyer) and Lipanthyl® Supra (i.e., the above-identified application) have very different dissolution profiles — both for the extent and for the rate. Lipanthyl® Supra presented a complete dissolution of fenofibrate within 1 hour whereas Lipanthyl® 250 only released 4% fenofibrate (i.e., 10 mg) within 1 hour.

13. It is my opinion that the claimed invention has a superior dissolution profile when compared to the dissolution profile of U.S. Patent No. 4,800,079 to Boyer.

14. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements so made are punishable by fine or imprisonment or both under § 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity or enforceability of the present application or any patent issued thereon.

Philippe Réginault

June 16th, 2003
Date

SEALED DOCUMENT

SEALED DOCUMENT

UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: Stamm et al

Application No. 09/899,026 Group Art Unit: 1615

Filed: July 6, 2001 Examiner: H. Sheikh

For: Fenofibrate Pharmaceutical Composition Having High Bioavailability and Method for Preparing It

Docket No: 107664.115US3

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Declaration under 37 CFR § 1.132 by Pascale Blouquin

I, Pascale Blouquin, declare:

1. I am Head of Formulation Development at Laboratoires Fournier, SA, the assignee of US Application No. 09/899,026 (hereafter "the above-identified application").

2. To the best of my knowledge, understanding and belief, Laboratories Fournier, SA, is the assignee of the above-identified application and of co-pending US Application Nos. 10/290,333, 10/665,520, 10/665,516, 10/665,519, 10/665,518, 10/665,517 and 10/665,522 (hereafter "the co-pending applications").

3. To the best of my knowledge, understanding and belief, the specification of the above-identified application is the same as the specification of the co-pending applications.

4. To the best of my knowledge, understanding and belief, Laboratories Fournier's Lab Notebook No. 1 (attached as Exhibit 1) and Laboratories Fournier's Lab Notebook No. 2 (attached as Exhibit 2) were transmitted around June 2004 to the counsel for Laboratoires Fournier at its request during document production for pending litigations related to Laboratoires Fournier's issued fenofibrate patents. This was the first time I had been asked to transmit to the counsel of Laboratoires Fournier these Lab Notebooks.

5. A certified English language translation of Lab Notebook No. 1 is attached as Exhibit 3; and a certified English language translation of Lab Notebook No. 2 is attached as Exhibit 4.

7. I have read and understand the contents of Lab Notebook Nos. 1 and 2.

8. Lab Notebook No. 1 covers the time period of 18 February 1997 to 15 May 1997.

9. Lab Notebook No. 2 covers the time period of 16 May 1997 to 30 July 1997.

10. To the best of my knowledge, understanding and belief, Lab Notebook Nos. 1 and 2 contain dissolution data of experiments conducted for the scale-up and development of the fenofibrate compositions of the invention described in the above-identified application and the co-pending applications.

11. To the best of my knowledge, understanding and belief, Lab Notebook Nos. 1 and 2 also contain dissolution data of capsules comprising 200 mg fenofibrate in various dissolution media.

12. The Examiner's attention is specifically directed to the dissolution data of Commercial Lot No. 2177 as follows:

(a) Example 2 and Figures 1 and 2 in the above-identified application and the co-pending applications provide the dissolution profile for a capsule comprising 200 mg fenofibrate from Commercial Lot No. 2177 in a dissolution medium constituted by water with 2% by weight Polysorbate 80 as measured using the rotating paddle method at 75 rpm, using the European Pharmacopoeia paddle apparatus.

(b) Lab Notebook No. 1 at Fournier Bates No. 1001569 provides the dissolution data for a capsule comprising 200 mg fenofibrate from Commercial Lot No. 2177 in a dissolution medium constituted by water with 0.025 M sodium lauryl sulfate as measured using the rotating paddle method at 75 rpm, using the European Pharmacopoeia paddle apparatus.

These results of Commercial Lot No. 2177 are shown in Table 1 below.

Table 1

	5 minutes	10 minutes	20 minutes	30 minutes	60 minutes	120 minutes
Lot No. 2177 in Above-Identified Application and the Co-Pending Applications in Example 2 in dissolution medium constituted by water with 2% by weight Polysorbate 80	0%	3.7%	16.5%	54.9%	not measured	not measured
Lot No. 2177 in Lab Notebook 1 at Fournier Bates No. 1001569 in a dissolution medium constituted by water with 0.025 M sodium lauryl sulfate	1.6%	19.7%	55.5%	67.7%	78.0%	85.5%

13. A summary of the dissolution data of the capsules comprising 200 mg fenofibrate from Lab Notebook Nos. 1 and 2 is shown in Table 2 below. The dissolution medium used are shown in Table 3.

Table 2

Fournier Bates No.	Dissolution Medium	5 min.	10 min.	20 min.	30 min	60 min	120 min
1001532	A	no data	26.8	46.4	56.5	no data	no data
1001532	B	6.5	24.7	43.4	53.3	64.4	75.7
1001532	C	7.1	30.2	52.2	62.9	75.9	83.5
1001560	C	3.4	19.1	52.0	65.7	78.5	86.8
1001562	C	0.8	9.8	46.8	63.0	79.7	88.4
1001566	C	1.8	13.5	50.1	66.0	82.3	88.3
1001569	C	1.6	19.7	55.5	67.7	78.0	85.5
1001653	C	4.8	23.1	55.4	66.8	no data	88.0
1001662	C	2.9	20.2	54.3	66.7	79.4	87.2
1001672	C	3.7	21.7	54.3	66.3	80.1	88.1
1001679	C	5.1	28.5	57.0	68.2	80.8	88.2
1001689	C	5.3	29.8	55.4	65.6	75.7	84.5

Fournier Bates No.	Dissolution Medium	5 min.	10 min.	20 min.	30 min	60 min	120 min
1001692	C	4.9	28.2	57.1	67.0	79.0	83.8
1001703	C	1.3	11.4	50.6	63.4	76.2	84.9
1001707	C	4.4	21.7	53.5	66.0	79.4	87.9
1001711	C	4.6	22.5	55.3	66.8	80.3	87.9
1001715	C	4.6	24.3	54.9	66.2	78.4	87.8
1001849	D	no data	26.3	76.1	88.0	98.4	102.6

Table 3

Dissolution Medium	Characteristic of Dissolution Medium
A	dissolution medium constituted by water with 2% by weight Polysorbate 80 using the rotating paddle method at 75 rpm according to the European Pharmacopoeia
B	dissolution medium constituted by water with 0.02 M sodium lauryl sulfate using the rotating paddle method at 75 rpm according to the European Pharmacopoeia
C	dissolution medium constituted by water with 0.025 M sodium lauryl sulfate using the rotating paddle method at 75 rpm according to the European Pharmacopoeia
D	dissolution medium constituted by water with 0.1 M sodium lauryl sulfate using the rotating paddle method at 90 rpm according to the European Pharmacopoeia

14. In my opinion, the claimed invention in the above-identified application and the copending applications has superior properties when compared to the dissolution data in the Laboratory Notebooks submitted herewith. A comparison of the pending claims, the Inventive Example 2 in the present application, the comparative Example 2 in the present application that is Lipanthyl® 200M from Lot No. 2177, and the dissolution data in the attached Laboratory Notebook No. 1 at Bates Number Fournier 1001569, which is also representative of Lipanthyl® 200M from Lot No. 2177, is set forth in the table below.

Time	% Dissolution Recited in Pending Claims	% Dissolution by Inventive Example 2 in the Application	% Dissolution of Lipanthyl® 200M from Lot No. 2177 in Lab Notebook No. 1 at Fournier No. 1001569	% Dissolution of Lipanthyl® 200M from Lot No. 2177 in Example 2 in the Application
30 minutes	at least 75	95.9	67.7	54.9
60 minutes	--	--	78.0	--

15. The claimed invention requires at least 75% dissolution in 30 minutes. The data in the attached Laboratory Notebook No. 1 shows that it takes almost 60 minutes for the Lipanthyl® 200M, to achieve a dissolution of 78%. In other words, it takes almost twice as long for Lipanthyl® 200M to achieve a dissolution that the claimed invention requires in 30 minutes. In view of these results, it is my opinion that the dissolution profile of the inventive example 2 in the Application is clearly faster than the dissolution profile of Lipanthyl® 200M.

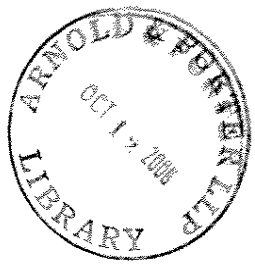
16. I was also asked to review Quality Assurance documents (attached as Exhibit 5) that are analysis certificates of different batches of product. In the analysis certificates, dissolution results are mentioned. The dissolution was done in 0.1 M SLS. The dissolution of fenofibrate in 0.1M SLS is much more faster than the dissolution in 0.025 M SLS, as the 0.1M SLS medium contains 4 times more SLS than a 0.025 SLS medium, and furthermore was done at higher speed.

17. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements so made are punishable by fine or imprisonment or both under § 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity or enforceability of the present application or any patent issued thereon.

P. Blouquin
Pascale Blouquin

Feb, 4th 2005
Date

PDR®
60
EDITION
2006



PHYSICIANS' DESK REFERENCE®

Senior Vice President, PDR Sales and Marketing: Dikran N. Barsamian
Vice President, Product Management: William T. Hicks
Vice President, Regulatory Affairs: Mukesh Mehta, RPh
Vice President, PDR Services: Brian Holland
Senior Directors, Pharmaceutical Solutions Sales: Chantal Corcos, Anthony Sorce
National Solutions Managers: Frank Karkowsky, Marion Reid, RPh
Senior Solutions Managers: Debra Goldman, Elaine Musco, Warner Stuart, Suzanne E. Yarrow, RN
Solutions Managers: Eileen Bruno, Cory Coleman, Marjorie A. Jaxel, Kevin McGlynn, Lois Smith, Richard Zwickel
Sales Coordinators: Arlene Phayre, Janet Wallendal

Senior Director, Brand and Product Management: Valerie E. Berger
Associate Product Managers: Michael Casale, Andrea Colavecchio
Senior Director, Publishing Sales and Marketing: Michael Bennett
Director, Trade Sales: Bill Gaffney
Associate Director, Marketing: Jennifer M. Fronzaglia
Senior Marketing Manager: Kim Marich
Direct Mail Manager: Lorraine M. Loening
Manager, Marketing Analysis: Dina A. Maeder
Promotion Manager: Linda Levine

Director of Operations: Robert Klein
Director, PDR Operations: Jeffrey D. Schaefer
Director of Finance: Mark S. Ritchin

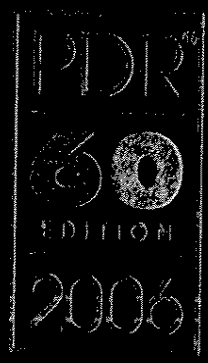
Director, Client Services: Stephanie Struble
Director, Clinical Content: Thomas Fleming, PharmD
Director, Editorial Services: Bette LaGow

Drug Information Specialists: Michael DeLuca, PharmD, MBA; Kajal Solanki, PharmD; Greg Tallis, RPh
Project Editors: Neil Chesanow, Harris Fleming
Senior Editor: Lori Murray
Senior Production Editor: Gwynned L. Kelly

Manager, Production Purchasing: Thomas Westburgh
PDR Production Manager: Steven Maher
Production Manager: Gayle Graizzaro
Production Specialist: Christina Klinger
Senior Production Coordinators: Gianna Caradonna, Yasmin Hernández
Production Coordinator: Nick W. Clark
Senior Index Editors: Noel Deloughery, Shannon Reilly
Format Editor: Michelle G. Auffant
Traffic Assistant: Kim Condon

Production Design Supervisor: Adeline Rich
Senior Electronic Publishing Designer: Livio Udina
Electronic Publishing Designers: Bryan C. Dix, Carrie Faeth, Monika Popowitz
Production Associate: Joan K. Akerlind
Digital Imaging Manager: Christopher Husted
Digital Imaging Coordinator: Michael Labruyere

ISBN: 1-56363-526-7



www.PDR.net

mobilePDR

PHYSICIANS' DESK REFERENCE®

Casodex—Cont.

caution should be exercised when CASODEX is administered to a nursing woman.

Pediatric Use: Safety and effectiveness of CASODEX in pediatric patients have not been established.

ADVERSE REACTIONS

In patients with advanced prostate cancer treated with CASODEX in combination with an LHRH analogue, the most frequent adverse experience was hot flashes (53%).

In the multicenter, double-blind, controlled clinical trial comparing CASODEX 50 mg once daily with flutamide 250 mg three times a day, each in combination with an LHRH analogue, the following adverse experiences with an incidence of 5% or greater, regardless of causality, have been reported.

Table 2
Incidence of Adverse Events
(≥ 5% in Either Treatment Group)
Regardless of Causality

Body System Adverse Event	Treatment Group Number of Patients (%)	
	CASODEX Plus LHRH Analogue (n = 401)	Flutamide Plus LHRH Analogue (n = 407)
Body as a Whole		
Pain (General)	142 (35)	127 (31)
Back Pain	102 (25)	105 (26)
Asthenia	89 (22)	87 (21)
Pelvic Pain	85 (21)	70 (17)
Infection	71 (18)	57 (14)
Abdominal Pain	46 (11)	46 (11)
Chest Pain	34 (8)	34 (8)
Headache	29 (7)	27 (7)
Flu Syndrome	28 (7)	30 (7)
Cardiovascular		
Hot Flashes	211 (53)	217 (53)
Hypertension	34 (8)	29 (7)
Digestive		
Constipation	87 (22)	69 (17)
Nausea	62 (15)	58 (14)
Diarrhea	49 (12)	107 (26)
Increased Liver Enzyme Test†	30 (7)	46 (11)
Dyspepsia	30 (7)	23 (6)
Flatulence	26 (6)	22 (5)
Anorexia	25 (6)	29 (7)
Vomiting	24 (6)	32 (8)
Hemic and Lymphatic		
Anemia††	45 (11)	53 (13)
Metabolic and Nutritional		
Peripheral Edema	53 (13)	42 (10)
Weight Loss	30 (7)	39 (10)
Hyperglycemia	26 (6)	27 (7)
Alkaline Phosphatase Increased	22 (5)	24 (6)
Weight Gain	22 (5)	18 (4)
Musculoskeletal		
Bone Pain	37 (9)	43 (11)
Myasthenia	27 (7)	19 (5)
Arthritis	21 (5)	29 (7)
Pathological Fracture	17 (4)	32 (8)
Nervous System		
Dizziness	41 (10)	35 (9)
Paresthesia	31 (8)	40 (10)
Insomnia	27 (7)	39 (10)
Anxiety	20 (5)	9 (2)
Depression	16 (4)	33 (8)
Respiratory System		
Dyspnea	51 (13)	32 (8)
Cough Increased	33 (8)	24 (6)
Pharyngitis	32 (8)	23 (6)
Bronchitis	24 (6)	22 (3)
Pneumonia	18 (4)	19 (5)
Rhinitis	15 (4)	22 (5)
Skin and Appendages		
Rash	35 (9)	30 (7)
Sweating	25 (6)	20 (5)
Urogenital		
Nocturia	49 (12)	55 (14)
Hematuria	48 (12)	26 (6)
Urinary Tract Infection	35 (9)	36 (9)
Gynecomastia	36 (9)	30 (7)
Impotence	27 (7)	35 (9)
Breast Pain	23 (6)	15 (4)
Urinary Frequency	23 (6)	29 (7)
Urinary Retention	20 (5)	14 (3)
Urination Impaired	19 (5)	15 (4)
Urinary Incontinence	15 (4)	32 (8)

†Increased liver enzyme test includes increases in AST, ALT or both.

††Anemia includes anemia, hypochromic- and iron deficiency anemia.

Other adverse experiences (greater than or equal to 2%, but less than 5%) reported in the CASODEX-LHRH analogue treatment group are listed below by body system and are in order of decreasing frequency within each body system regardless of causality.

Body as a Whole: Neoplasm; Neck pain; Fever; Chills; Sepsis; Hernia; Cyst

Cardiovascular: Angina pectoris; Congestive heart failure; Myocardial infarct; Heart arrest; Coronary artery disorder; Syncope

Digestive: Melena; Rectal hemorrhage; Dry mouth; Dysphagia; Gastrointestinal disorder; Periodontal abscess; Gastrointestinal carcinoma

Metabolic and Nutritional: Edema; Bun increased; Creatinine increased; Dehydration; Gout; Hypercholesteremia

Musculoskeletal: Myalgia; Leg cramps

Nervous: Hypertonia; Confusion; Somnolence; Libido decreased; Neuropathy; Nervousness

Respiratory: Lung disorder; Asthma; Epistaxis; Sinusitis

Skin and Appendages: Dry skin; Alopecia; Pruritus; Herpes zoster; Skin carcinoma; Skin disorder

Special Senses: Cataract specified

Urogenital: Dysuria; Urinary urgency; Hydronephrosis; Urinary tract disorder

Abnormal Laboratory Test Values: Laboratory abnormalities including elevated AST, ALT, bilirubin, BUN, and creatinine and decreased hemoglobin and white cell count have been reported in both CASODEX-LHRH analogue treated and flutamide-LHRH analogue treated patients.

Postmarketing Experience: Rare cases of interstitial pneumonitis and pulmonary fibrosis have been reported with CASODEX.

OVERDOSAGE

Long-term clinical trials have been conducted with dosages up to 200 mg of CASODEX daily and these dosages have been well tolerated. A single dose of CASODEX that results in symptoms of an overdose considered to be life-threatening has not been established.

There is no specific antidote; treatment of an overdose should be symptomatic.

In the management of an overdose with CASODEX, vomiting may be induced if the patient is alert. It should be remembered that, in this patient population, multiple drugs may have been taken. Dialysis is not likely to be helpful since CASODEX is highly protein bound and is extensively metabolized. General supportive care, including frequent monitoring of vital signs and close observation of the patient, is indicated.

DOSAGE AND ADMINISTRATION

The recommended dose for CASODEX therapy in combination with an LHRH analogue is one 50 mg tablet once daily (morning or evening), with or without food. It is recommended that CASODEX be taken at the same time each day. Treatment with CASODEX should be started at the same time as treatment with an LHRH analogue.

Dosage Adjustment in Renal Impairment: No dosage adjustment is necessary for patients with renal impairment (see CLINICAL PHARMACOLOGY, Special Populations, Renal Insufficiency).

Dosage Adjustment in Hepatic Impairment: No dosage adjustment is necessary for patients with mild to moderate hepatic impairment. Although there is a 76% (5.9 and 10.4 days for normal and impaired patients, respectively) increase in the half-life of the active enantiomer of bicalutamide in patients with severe liver impairment (n=4), no dosage adjustment is necessary (see CLINICAL PHARMACOLOGY, Special Populations, Hepatic Impairment, PRECAUTIONS and WARNINGS sections).

HOW SUPPLIED

50 mg Tablets. (NDC 0310-0705) White, film-coated tablets (identified on one side with "CDX50" and on the reverse with the "CASODEX logo") are supplied in unit dose blisters of 30 tablets per carton (0310-0705-39), bottles of 30 tablets (0310-0705-30) and bottles of 100 tablets (0310-0705-10). Store at controlled room temperature, 20-25°C (68-77°F).

AstraZeneca
Manufactured for
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850
By: IPR Pharmaceuticals Inc.
Carolina, PR 00984
Made in USA
Rev 11-03 PCC 690200

Shown in Product Identification Guide, page 306

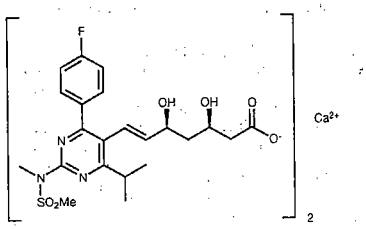
CEFOTAN® ℞
[*cef 'o-tan*]
(cefotetan disodium for injection)
For Intravenous or Intramuscular Use

CEFOTAN® ℞
(cefotetan injection)
In GALAXY® Plastic Container (PL 2040)
For Intravenous Use Only

CRESTOR® ℞
[*krĕs-tōr*]
(rosuvastatin calcium)

DESCRIPTION

CRESTOR® (rosuvastatin calcium) is a synthetic lipid-lowering agent. Rosuvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis. Rosuvastatin calcium is bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino] pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt. The empirical formula for rosuvastatin calcium is $(C_{22}H_{27}FN_3O_6S)_2Ca$. Its molecular weight is 1001.14. Its structural formula is:



Rosuvastatin calcium is a white amorphous powder that is sparingly soluble in water and methanol, and slightly soluble in ethanol. Rosuvastatin is a hydrophilic compound with a partition coefficient (octanol/water) of 0.13 at pH of 7.0.

CRESTOR Tablets for oral administration contain 5, 10, 20, or 40 mg of rosuvastatin and the following inactive ingredients: microcrystalline cellulose NF, lactose monohydrate NF, tribasic calcium phosphate NF, crospovidone NF, magnesium stearate NF, hypromellose NF, triacetin NF, titanium dioxide USP, yellow ferric oxide, and red ferric oxide NF.

CLINICAL PHARMACOLOGY

General: In the bloodstream, cholesterol and triglycerides (TG) circulate as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and low-density lipoprotein (LDL) fractions that contain apolipoprotein B-100 (ApoB-100) and high-density lipoprotein (HDL) fractions.

Cholesterol and TG synthesized in the liver are incorporated into VLDL and secreted into the circulation for delivery to peripheral tissues. TG are removed by the action of lipases, and in a series of steps, the modified VLDL is transformed first into IDL and then into cholesterol-rich LDL. IDL and LDL are removed from the circulation mainly by high affinity ApoB/E receptors, which are expressed to the greatest extent on liver cells. HDL is hypothesized to participate in the reverse transport of cholesterol from tissues back to the liver.

Epidemiologic, experimental, and clinical studies have established that high LDL cholesterol (LDL-C), low HDL cholesterol (HDL-C), and high plasma TG promote human atherosclerosis and are risk factors for developing cardiovascular disease. In contrast, higher levels of HDL-C are associated with decreased cardiovascular risk.

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, IDL, and remnants, can also promote atherosclerosis. Elevated plasma triglycerides are frequently found with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease (CHD). As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

Mechanism of Action: Rosuvastatin is a selective and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor of cholesterol. *In vivo* studies in animals, and *in vitro* studies in cultured animal and human cells have shown rosuvastatin to have a high uptake into, and selectivity for, action in the liver, the target organ for cholesterol lowering. In *in vivo* and *in vitro* studies, rosuvastatin produces its lipid-modifying effects in two ways. First, it increases the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL. Second, rosuvastatin inhibits hepatic synthesis of VLDL, which reduces the total number of VLDL and LDL particles. Rosuvastatin reduces total cholesterol (total-C), LDL-C, ApoB, and nonHDL-C (total cholesterol minus HDL-C) in patients with homozygous and heterozygous familial hypercholesterolemia (FH), nonfamilial forms of hypercholesterolemia, and mixed dyslipidemia. Rosuvastatin also reduces TG and produces increases in HDL-C. Rosuvastatin reduces total-C, LDL-C, VLDL-cholesterol (VLDL-C), ApoB, nonHDL-C, and TG, and increases HDL-C in patients with isolated hypertriglyceridemia. The effect of rosuvastatin on cardiovascular morbidity and mortality has not been determined.

Pharmacokinetics and Drug Metabolism

Absorption: In clinical pharmacology studies in man, peak plasma concentrations of rosuvastatin were reached 3 to 5 hours following oral dosing. Both peak concentration (C_{max}) and area under the plasma concentration-time curve (AUC) increased in approximate proportion to rosuvastatin dose. The absolute bioavailability of rosuvastatin is approximately 20%.

Administration of rosuvastatin with food decreased the rate of drug absorption by 20% as assessed by C_{max}, but there was no effect on the extent of absorption as assessed by AUC.

Plasma concentrations of rosuvastatin do not differ following evening or morning drug administration.
Significant LDL-C reductions are seen when rosuvastatin is given with or without food, and regardless of the time of day of drug administration.
Distribution: Mean volume of distribution at steady-state of rosuvastatin is approximately 134 liters. Rosuvastatin is 88% bound to plasma proteins, mostly albumin. This binding is reversible and independent of plasma concentrations.
Metabolism: Rosuvastatin is not extensively metabolized; approximately 10% of a radiolabeled dose is recovered as metabolite. The major metabolite is N-desmethyl rosuvastatin, which is formed principally by cytochrome P450 2C9, and *in vitro* studies have demonstrated that N-desmethyl rosuvastatin has approximately one-sixth to one-half the HMG-CoA reductase inhibitory activity of rosuvastatin. Overall, greater than 90% of active plasma HMG-CoA reductase inhibitory activity is accounted for by rosuvastatin.
Excretion: Following oral administration, rosuvastatin and its metabolites are primarily excreted in the feces (90%). The elimination half-life ($t_{1/2}$) of rosuvastatin is approximately 19 hours.
After an intravenous dose, approximately 28% of total body clearance was via the renal route, and 72% by the hepatic route.

Special Populations

Race: A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics among Caucasian, Hispanic, and Black or Afro-Caribbean groups. However, pharmacokinetic studies, including one conducted in the US, have demonstrated an approximate 2-fold elevation in median exposure (AUC and C_{max}) in Asian subjects when compared with a Caucasian control group (see WARNINGS, Myopathy/Rhabdomyolysis, PRECAUTIONS, General and DOSAGE AND ADMINISTRATION).
Gender: There were no differences in plasma concentrations of rosuvastatin between men and women.
Geriatric: There were no differences in plasma concentrations of rosuvastatin between the nonelderly and elderly populations (age ≥65 years).
Pediatric: In a pharmacokinetic study, 18 patients (9 boys and 9 girls) 10 to 17 years of age with heterozygous FH received single and multiple oral doses of rosuvastatin. Both C_{max} and AUC of rosuvastatin were similar to values observed in adult subjects administered the same doses.
Renal Insufficiency: Mild to moderate renal impairment (creatinine clearance ≥ 30 mL/min/1.73m^2) had no influence on plasma concentrations of rosuvastatin when oral doses of 20 mg rosuvastatin were administered for 14 days. However, plasma concentrations of rosuvastatin increased to a clinically significant extent (about 3-fold) in patients with severe renal impairment (CL_{cr} < 30 mL/min/1.73m^2) compared with healthy subjects (CL_{cr} > 80 mL/min/1.73m^2) (see PRECAUTIONS, General).
Hemodialysis: Steady-state plasma concentrations of rosuvastatin in patients on chronic hemodialysis were approximately 50% greater compared with healthy volunteer subjects with normal renal function.
Hepatic Insufficiency: In patients with chronic alcohol liver disease, plasma concentrations of rosuvastatin were modestly increased. In patients with Child-Pugh A disease, C_{max} and AUC were increased by 60% and 5%, respectively, as compared with patients with normal liver function. In patients with Child-Pugh B disease, C_{max} and AUC were increased 100% and 21%, respectively, compared with patients with normal liver function (see CONTRAINDICATIONS and WARNINGS, Liver Enzymes).

Drug-Drug Interactions

Cytochrome P450 3A4: *In vitro* and *in vivo* data indicate that rosuvastatin clearance is not dependent on metabolism by cytochrome P450 3A4 to a clinically significant extent. This has been confirmed in studies with known cytochrome P450 3A4 inhibitors (ketoconazole, erythromycin, itraconazole).
Ketoconazole: Coadministration of ketoconazole (200 mg twice daily for 7 days) with rosuvastatin (80 mg) resulted in no change in plasma concentrations of rosuvastatin.
Erythromycin: Coadministration of erythromycin (500 mg four times daily for 7 days) with rosuvastatin (80 mg) decreased AUC and C_{max} of rosuvastatin by 20% and 31%, respectively. These reductions are not considered clinically significant.
Itraconazole: Itraconazole (200 mg once daily for 5 days) resulted in a 39% and 28% increase in AUC of rosuvastatin after 10 mg and 80 mg dosing, respectively. These increases are not considered clinically significant.
Fluconazole: Coadministration of fluconazole (200 mg once daily for 11 days) with rosuvastatin (80 mg) resulted in a 14% increase in AUC of rosuvastatin. This increase is not considered clinically significant.
Cyclosporine: Coadministration of cyclosporine with rosuvastatin resulted in no significant changes in cyclosporine plasma concentrations. However, C_{max} and AUC of rosuvastatin increased 11- and 7-fold, respectively, compared with historical data in healthy subjects. These increases are considered to be clinically significant (see PRECAUTIONS Drug Interactions, WARNINGS, Myopathy/Rhabdomyolysis, and DOSAGE AND ADMINISTRATION).
Warfarin: Coadministration of warfarin (25 mg) with rosuvastatin (40 mg) did not change warfarin plasma concentrations but increased the International Normalized Ratio (INR) (see PRECAUTIONS, Drug Interactions).
Digoxin: Coadministration of digoxin (0.5 mg) with rosuvastatin (40 mg) resulted in no change to digoxin plasma concentrations.
Fenofibrate: Coadministration of fenofibrate (67 mg three times daily) with rosuvastatin (10 mg) resulted in no significant changes in plasma concentrations of rosuvastatin or fenofibrate (see PRECAUTIONS, Drug Interactions, and WARNINGS, Myopathy/Rhabdomyolysis).
Gemfibrozil: Coadministration of gemfibrozil (600 mg twice daily for 7 days) with rosuvastatin (80 mg) resulted in a 90% and 120% increase for AUC and C_{max} of rosuvastatin, respectively. This increase is considered to be clinically significant (see PRECAUTIONS, Drug Interactions, WARNINGS, Myopathy/Rhabdomyolysis, DOSAGE AND ADMINISTRATION).
Antacid: Coadministration of an antacid (aluminum and magnesium hydroxide combination) with rosuvastatin (40 mg) resulted in a decrease in plasma concentrations of rosuvastatin by 54%. However, when the antacid was given 2 hours after rosuvastatin, there were no clinically significant changes in plasma concentrations of rosuvastatin (see PRECAUTIONS, Information for Patients).
Oral contraceptives: Coadministration of oral contraceptives (ethinyl estradiol and norgestrel) with rosuvastatin resulted in an increase in plasma concentrations of ethinyl estradiol and norgestrel by 26% and 34%, respectively.

Clinical Studies

Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Type IIa and IIb)

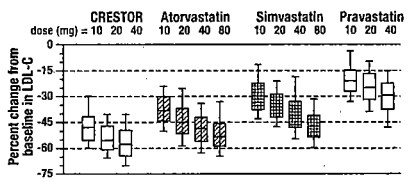
CRESTOR reduces total-C, LDL-C, ApoB, nonHDL-C, and TG, and increases HDL-C, in patients with hypercholesterolemia and mixed dyslipidemia. Therapeutic response is seen within 1 week, and maximum response is usually achieved within 4 weeks and maintained during long-term therapy.
CRESTOR is effective in a wide variety of adult patient populations with hypercholesterolemia, with and without hypertriglyceridemia, regardless of race, gender, or age and in special populations such as diabetics or patients with heterozygous FH. Experience in pediatric patients has been limited to patients with homozygous FH.
Dose-Ranging Study: In a multicenter, double-blind, placebo-controlled, dose-ranging study in patients with hypercholesterolemia, CRESTOR given as a single daily dose for 6 weeks significantly reduced total-C, LDL-C, nonHDL-C, and ApoB, across the dose range (Table 1).

Table 1.
Dose-Response in Patients With Primary Hypercholesterolemia (Adjusted Mean % Change From Baseline at Week 6)

Dose	N	Total-C	LDL-C	Non HDL-C	ApoB	TG	HDL-C
Placebo	13	-5	-7	-7	-3	-3	3
5	17	-33	-45	-44	-38	-35	13
10	17	-36	-52	-48	-42	-10	14
20	17	-40	-55	-51	-46	-23	8
40	18	-46	-63	-60	-54	-28	10

Active-Controlled Study: CRESTOR was compared with the HMG-CoA reductase inhibitors atorvastatin, simvastatin, and pravastatin in a multicenter, open-label, dose-ranging study of 2,240 patients with Type IIa and IIb hypercholesterolemia. After randomization, patients were treated for 6 weeks with a single daily dose of either CRESTOR, atorvastatin, simvastatin, or pravastatin (Figure 1 and Table 2).

Figure 1.
Percent LDL-C Change by Dose of CRESTOR, Atorvastatin, Simvastatin, and Pravastatin at Week 6 in Patients With Type IIa/IIb Dyslipidemia



Box plots are a representation of the 25th, 50th, and 75th percentile values, with whiskers representing the 10th and 90th percentile values.
Mean baseline LDL-C: 189 mg/dL.

Table 2.
Percent Change in LDL-C From Baseline to Week 6 (LS means[§]) by Treatment Group (sample sizes ranging from 156–157 patients per group)

Treatment	Treatment Daily Dose 10 mg	20 mg	40 mg	80 mg
CRESTOR	-46*	-52†	-55‡	—
Atorvastatin	-37	-43	-48	-51
Pravastatin	-20	-24	-30	—
Simvastatin	-28	-35	-39	-46

*CRESTOR 10 mg reduced LDL-C significantly more than atorvastatin 10 mg; pravastatin 10 mg, 20 mg, and 40 mg; simvastatin 10 mg, 20 mg, and 40 mg. ($p<0.002$)
†CRESTOR 20 mg reduced LDL-C significantly more than atorvastatin 20 mg and 40 mg; pravastatin 20 mg and 40 mg; simvastatin 20 mg, 40 mg, and 80 mg. ($p<0.002$)
‡CRESTOR 40 mg reduced LDL-C significantly more than atorvastatin 40 mg; pravastatin 40 mg; simvastatin 40 mg and 80 mg. ($p<0.002$)
§Corresponding standard errors are approximately 1.00

Heterozygous Familial Hypercholesterolemia

In a study of patients with heterozygous FH (baseline mean LDL of 291), patients were randomized to CRESTOR 20 mg or atorvastatin 20 mg. The dose was increased by 6-week intervals. Significant LDL-C reductions from baseline were seen at each dose in both treatment groups (Table 3).
[See table 3 below]

Hypertriglyceridemia (Fredrickson Type IIb & IV)

In a double-blind, placebo-controlled dose-response study in patients with baseline TG levels from 273 to 817 mg/dL, CRESTOR given as a single daily dose (5 to 40 mg) over 6 weeks significantly reduced serum TG levels (Table 4).
[See table 4 at top of next page]

Homozygous Familial Hypercholesterolemia

In an open-label, forced-titration study, homozygous FH patients (n=40, 8-63 years) were evaluated for their response to CRESTOR 20 to 40 mg titrated at a 6-week interval. In the overall population, the mean LDL-C reduction from baseline was 22%. About one-third of the patients benefited from increasing their dose from 20 mg to 40 mg with further LDL lowering of greater than 6%. In the 27 patients with at least a 15% reduction in LDL-C, the mean LDL-C reduction was 30% (median 28% reduction). Among 13 patients with an LDL-C reduction of <15%, 3 had no change or an increase in LDL-C. Reductions in LDL-C of 15% or greater were observed in 3 of 5 patients with known receptor negative status.

INDICATIONS AND USAGE

CRESTOR is indicated:
1. as an adjunct to diet to reduce elevated total-C, LDL-C, ApoB, nonHDL-C, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Type IIa and IIb);
2. as an adjunct to diet for the treatment of patients with elevated serum TG levels (Fredrickson Type IV);
3. to reduce LDL-C, total-C, and ApoB in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

According to NCEP-ATPIII guidelines, therapy with lipid-altering agents should be a component of multiple-risk-factor intervention in individuals at increased risk for coronary heart disease due to hypercholesterolemia. The two major modalities of LDL-lowering therapy are therapeutic lifestyle changes (TLC) and drug therapy. The TLC Diet stresses reductions in saturated fat and cholesterol intake. Table 5 defines LDL-C goals and cutpoints for initiation of TLC and for drug consideration.
[See table 5 at top of next page]
After the LDL-C goal has been achieved, if the TG is still ≥ 200 mg/dL, nonHDL-C (total-C minus HDL-C) becomes a secondary target of therapy. NonHDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk category.
At the time of hospitalization for a coronary event, consideration can be given to initiating drug therapy at discharge if the LDL-C is ≥ 130 mg/dL (see NCEP Treatment Guidelines, above).
Patients >20 years of age should be screened for elevated cholesterol levels every 5 years.
Prior to initiating therapy with CRESTOR, secondary causes for hypercholesterolemia (e.g., poorly-controlled dia-

Continued on next page

Table 3.
Mean LDL-C Percentage Change from Baseline

		CRESTOR (n=435) LS Mean* (95% CI)	Atorvastatin (n=187) LS Mean (95% CI)
Week 6	20 mg	-47% (-49%, -46%)	-38% (-40%, -36%)
Week 12	40 mg	-55% (-57%, -54%)	-47% (-49%, -45%)
Week 18	80 mg	NA	-52% (-54%, -50%)

*LS Means are least square means adjusted for baseline LDL.

Crestor—Cont.

betes mellitus, hypothyroidism, nephrotic syndrome, dysliproproteinemias, obstructive liver disease, other drug therapy, and alcoholism) should be excluded, and a lipid profile performed to measure total-C, LDL-C, HDL-C, and TG. For patients with TG <400 mg/dL (<4.5 mmol/L), LDL-C can be estimated using the following equation: LDL-C = total-C - (0.20 × [TG] + HDL-C). For TG levels >400 mg/dL (>4.5 mmol/L), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation.

CRESTOR has not been studied in Fredrickson Type I, III, and V dyslipidemias.

CONTRAINDICATIONS

CRESTOR is contraindicated in patients with a known hypersensitivity to any component of this product.

Rosuvastatin is contraindicated in patients with active liver disease or with unexplained persistent elevations of serum transaminases (see WARNINGS, Liver Enzymes).

Pregnancy and Lactation

Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. ROSUVASTATIN SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS. If the patient becomes pregnant while taking this drug, therapy should be discontinued immediately and the patient apprised of the potential hazard to the fetus.

WARNINGS

Liver Enzymes

HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. The incidence of persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more consecutive occasions) in serum transaminases in fixed dose studies was 0.4, 0, 0, and 0.1% in patients who received rosuvastatin 5, 10, 20, and 40 mg, respectively. In most cases, the elevations were transient and resolved or improved on continued therapy or after a brief interruption in therapy. There were two cases of jaundice, for which a relationship to rosuvastatin therapy could not be determined, which resolved after discontinuation of therapy. There were no cases of liver failure or irreversible liver disease in these trials.

It is recommended that liver function tests be performed before and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (e.g., semiannually) thereafter. Liver enzyme changes generally occur in the first 3 months of treatment with rosuvastatin. Patients who develop increased transaminase levels should be monitored until the abnormalities have resolved. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of rosuvastatin is recommended.

Rosuvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease (see CLINICAL PHARMACOLOGY, Special Populations, Hepatic Insufficiency). Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of rosuvastatin (see CONTRAINDICATIONS).

Myopathy/Rhabdomyolysis

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with rosuvastatin and with other drugs in this class.

Uncomplicated myalgia has been reported in rosuvastatin-treated patients (see ADVERSE REACTIONS). Creatine kinase (CK) elevations (>10 times upper limit of normal) occurred in 0.2% to 0.4% of patients taking rosuvastatin at doses up to 40 mg in clinical studies. Treatment-related myopathy, defined as muscle aches or muscle weakness in conjunction with increases in CK values >10 times upper limit of normal, was reported in up to 0.1% of patients taking rosuvastatin doses of up to 40 mg in clinical studies. In clinical trials, the incidence of myopathy and rhabdomyolysis increased at doses of rosuvastatin above the recommended dosage range (5 to 40 mg). In postmarketing experience, effects on skeletal muscle, e.g. uncomplicated myalgia, myopathy and, rarely, rhabdomyolysis have been reported in patients treated with HMG-CoA reductase inhibitors including rosuvastatin. As with other HMG-CoA reductase inhibitors, reports of rhabdomyolysis with rosuvastatin are rare, but higher at the highest marketed dose (40 mg). Factors that may predispose patients to myopathy with HMG-CoA reductase inhibitors include advanced age (≥65 years), hypothyroidism, and renal insufficiency.

Consequently:

1. Rosuvastatin should be prescribed with caution in patients with predisposing factors for myopathy, such as, renal impairment (see DOSAGE AND ADMINISTRATION), advanced age, and inadequately treated hypothyroidism.
2. Patients should be advised to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Rosuvastatin therapy should be discontinued if markedly elevated CK levels occur or myopathy is diagnosed or suspected.
3. The 40 mg dose of rosuvastatin is reserved only for those patients who have not achieved their LDL-C goal utilizing the 20 mg dose of rosuvastatin once daily (see DOSAGE AND ADMINISTRATION).
4. The risk of myopathy during treatment with rosuvastatin may be increased with concurrent administration of other lipid-lowering therapies or cyclosporine, (see CLINICAL PHARMACOLOGY, Drug Interactions, PRECAUTIONS, Drug Interactions, and DOSAGE AND ADMINISTRATION). **The benefit of further alterations in lipid levels by the combined use of rosuvastatin with fibrates or niacin should be carefully weighed against the potential risks of this combination. Combination therapy with rosuvastatin and gemfibrozil should generally be avoided. (See DOSAGE AND ADMINISTRATION and PRECAUTIONS, Drug Interactions).**
5. **The risk of myopathy during treatment with rosuvastatin may be increased in circumstances which increase rosuvastatin drug levels (see CLINICAL PHARMACOLOGY, Special Populations, Race and Renal Insufficiency, and PRECAUTIONS, General).**
6. **Rosuvastatin therapy should also be temporarily withheld in any patient with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., sepsis, hypotension, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, or uncontrolled seizures).**

PRECAUTIONS

General

Before instituting therapy with rosuvastatin, an attempt should be made to control hypercholesterolemia with appropriate diet and exercise, weight reduction in obese patients, and treatment of underlying medical problems (see INDICATIONS AND USAGE).

Administration of rosuvastatin 20 mg to patients with severe renal impairment (CL_{cr} <30 mL/min/1.73 m^2) resulted in a 3-fold increase in plasma concentrations of rosuvastatin compared with healthy volunteers (see WARNINGS, Myopathy/Rhabdomyolysis and DOSAGE AND ADMINISTRATION).

The result of a large pharmacokinetic study conducted in the US demonstrated an approximate 2-fold elevation in median exposure in Asian subjects (having either Filipino, Chinese, Japanese, Korean, Vietnamese or Asian-Indian origin) compared with a Caucasian control group. This increase should be considered when making rosuvastatin dosing decisions for Asian patients (see WARNINGS Myopathy/Rhabdomyolysis; CLINICAL PHARMACOLOGY, Special Populations, Race, and DOSAGE AND ADMINISTRATION).

Information for Patients

Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

When taking rosuvastatin with an aluminum and magnesium hydroxide combination antacid, the antacid should be taken at least 2 hours after rosuvastatin administration (see CLINICAL PHARMACOLOGY, Drug Interactions).

Laboratory Tests

In the rosuvastatin clinical trial program, dipstick-positive proteinuria and microscopic hematuria were observed among rosuvastatin treated patients, predominantly in patients dosed above the recommended dose range (i.e., 80 mg). However, this finding was more frequent in patients taking rosuvastatin 40 mg, when compared to lower doses of rosuvastatin or comparator statins, though it was generally transient and was not associated with worsening renal function. Although the clinical significance of this finding is unknown, a dose reduction should be considered for patients on rosuvastatin 40 mg therapy with unexplained persistent proteinuria during routine urinalysis testing.

Drug Interactions

Cyclosporine: When rosuvastatin 10 mg was coadministered with cyclosporine in cardiac transplant patients, rosuvastatin mean C_{max} and mean AUC were increased 11-fold and 7-fold, respectively, compared with healthy volunteers. These increases are considered to be clinically significant and require special consideration in the dosing of rosuvastatin to patients taking concomitant cyclosporine (see WARNINGS, Myopathy/Rhabdomyolysis, and DOSAGE AND ADMINISTRATION).

Warfarin: Coadministration of rosuvastatin to patients on stable warfarin therapy resulted in clinically significant rises in INR (>4, baseline 2-3). In patients taking coumarin anticoagulants and rosuvastatin concomitantly, INR should be determined before starting rosuvastatin and frequently enough during early therapy to ensure that no significant alteration of INR occurs. Once a stable INR time has been documented, INR can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of rosuvastatin is changed, the same procedure should be repeated. Rosuvastatin therapy has not been associated with bleeding or with changes in INR in patients not taking anticoagulants.

Gemfibrozil: Coadministration of a single rosuvastatin dose to healthy volunteers on gemfibrozil (600 mg twice daily) resulted in 2.2- and 1.9-fold, respectively, increase in mean C_{max} and mean AUC of rosuvastatin (see DOSAGE AND ADMINISTRATION).

Endocrine Function

Although clinical studies have shown that rosuvastatin alone does not reduce basal plasma cortisol concentration or impair adrenal reserve, caution should be exercised if any HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones such as ketoconazole, spironolactone, and cimetidine.

CNS Toxicity

CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with several other members of this drug class. A chemically similar drug in this class produced dose-dependent optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in dogs, at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans

Table 4.
Dose-Response in Patients With Primary Hypertriglyceridemia Over 6 Weeks
Dosing Median (Min, Max) Percent Change From Baseline

Dose	Placebo N=26	CRESTOR 5 mg N=25	CRESTOR 10 mg N=23	CRESTOR 20 mg N=27	CRESTOR 40 mg N=25
Triglycerides	1 (-40, 72)	-21 (-58, 38)	-37 (-65, 5)	-37 (-72, 11)	-43 (-80, -7)
NonHDL-C	2 (-13, 19)	-29 (-43, -8)	-49 (-59, -20)	-43 (-74, 12)	-51 (-62, -6)
VLDL-C	2 (-36, 53)	-25 (-62, 49)	-48 (-72, 14)	-49 (-83, 20)	-56 (-83, 10)
Total-C	1 (-13, 17)	-24 (-40, -4)	-40 (-51, -14)	-34 (-61, -11)	-40 (-51, -4)
LDL-C	5 (-30, 52)	-28 (-71, 2)	-45 (-59, 7)	-31 (-66, 34)	-43 (-61, -3)
HDL-C	-3 (-25, 18)	3 (-38, 33)	8 (-8, 24)	22 (-5, 50)	17 (-14, 63)

Table 5.
NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal	LDL level at which to initiate TLC	LDL level at which to consider drug therapy
CHD[a] or CHD Risk Equivalent (10-year risk > 20%)	<100 mg/dL	≥100 mg/dL	≥130 mg/dL (100-129 mg/dL: drug optional)[b]
2+ Risk Factors (10-year risk ≤ 20%)	<130 mg/dL	≥130 mg/dL	≥130 mg/dL 10-year risk 10-20%
			≥160 mg/dL 10-year risk <10%
0-1 Risk Factor[c]	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160-189 mg/dL (LDL-lowering drug optional)

[a] CHD = coronary heart disease.
[b] Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C <100 mg/dL cannot be achieved by TLC. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.
[c] Almost all people with 0-1 risk factor have 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

taking the highest recommended dose. Edema, hemorrhage, and partial necrosis in the interstitium of the choroid plexus was observed in a female dog sacrificed moribund at day 24 at 90 mg/kg/day by oral gavage (systemic exposures 100 times the human exposure at 40 mg/day based on AUC comparisons). Corneal opacity was seen in dogs treated for 52 weeks at 6 mg/kg/day by oral gavage (systemic exposures 20 times the human exposure at 40 mg/day based on AUC comparisons). Cataracts were seen in dogs treated for 12 weeks by oral gavage at 30 mg/kg/day (systemic exposures 60 times the human exposure at 40 mg/day based on AUC comparisons). Retinal dysplasia and retinal loss were seen in dogs treated for 4 weeks by oral gavage at 90 mg/kg/day (systemic exposures 100 times the human exposure at 40 mg/day based on AUC). Doses ≤30 mg/kg/day (systemic exposures ≤60 times the human exposure at 40 mg/day based on AUC comparisons) following treatment up to one year, did not reveal retinal findings.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 104-week carcinogenicity study in rats at dose levels of 2, 20, 60, or 80 mg/kg/day by oral gavage, the incidence of uterine stromal polyps was significantly increased in females at 80 mg/kg/day at systemic exposure 20 times the human exposure at 40 mg/day based on AUC. Increased incidence of polyps was not seen at lower doses.

In a 107-week carcinogenicity study in mice given 10, 60, 200 mg/kg/day by oral gavage, an increased incidence of hepatocellular adenoma/carcinoma was observed at 200 mg/kg/day at systemic exposures 20 times human exposure at 40 mg/day based on AUC. An increased incidence of hepatocellular tumors was not seen at lower doses.

Rosuvastatin was not mutagenic or clastogenic with or without metabolic activation in the Ames test with *Salmonella typhimurium* and *Escherichia coli*, the mouse lymphoma assay, and the chromosomal aberration assay in Chinese hamster lung cells. Rosuvastatin was negative in the *in vivo* mouse micronucleus test.

In rat fertility studies with oral gavage doses of 5, 15, 50 mg/kg/day, males were treated for 9 weeks prior to and throughout mating and females were treated 2 weeks prior to mating and throughout mating until gestation day 7. No adverse effect on fertility was observed at 50 mg/kg/day (systemic exposures up to 10 times human exposure at 40 mg/day based on AUC comparisons). In testicles of dogs treated with rosuvastatin at 30 mg/kg/day for one month, spermatidic giant cells were seen. Spermatidic giant cells were observed in monkeys after 6-month treatment at 30 mg/kg/day in addition to vacuolation of seminiferous tubular epithelium. Exposures in the dog were 20 times and in the monkey 10 times human exposure at 40 mg/day based on body surface area comparisons. Similar findings have been seen with other drugs in this class.

Pregnancy

Pregnancy Category X

See CONTRAINDICATIONS.

Rosuvastatin may cause fetal harm when administered to a pregnant woman. Rosuvastatin is contraindicated in women who are or may become pregnant. Safety in pregnant women has not been established. There are no adequate and well-controlled studies of rosuvastatin in pregnant women. Rosuvastatin crosses the placenta and is found in fetal tissue and amniotic fluid at 3% and 20%, respectively, of the maternal plasma concentration following a single 25 mg/kg oral gavage dose on gestation day 16 in rats. A higher fetal tissue distribution (25% maternal plasma concentration) was observed in rabbits after a single oral gavage dose of 1 mg/kg on gestation day 18. If this drug is administered to a woman with reproductive potential, the patient should be apprised of the potential hazard to a fetus.

In female rats given oral gavage doses of 5, 15, 50 mg/kg/day rosuvastatin before mating and continuing through day 7 postcoitus results in decreased fetal body weight (female pups) and delayed ossification at the high dose (systemic exposures 10 times human exposure at 40 mg/day based on AUC comparisons).

In pregnant rats given oral gavage doses of 2, 10, 50 mg/kg/day from gestation day 7 through lactation day 21 (weaning), decreased pup survival occurred in groups given 50 mg/kg/day, systemic exposures ≥12 times human exposure at 40 mg/day based on body surface area comparisons.

In pregnant rabbits given oral gavage doses of 0.3, 1, 3 mg/kg/day from gestation day 6 to lactation day 18 (weaning), exposures equivalent to human exposure at 40 mg/day based on body surface area comparisons, decreased fetal viability and maternal mortality was observed.

Rosuvastatin was not teratogenic in rats at ≤25 mg/kg/day or in rabbits ≤3 mg/kg/day (systemic exposures equivalent to human exposure at 40 mg/day based on AUC or body surface comparison, respectively).

Nursing Mothers

It is not known whether rosuvastatin is excreted in human milk. Studies in lactating rats have demonstrated that rosuvastatin is secreted into breast milk at levels 3 times higher than that obtained in the plasma following oral gavage dosing. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from rosuvastatin, a decision should be made whether to discontinue nursing or administration of rosuvastatin taking into account the importance of the drug to the lactating woman.

Pediatric Use

The safety and effectiveness in pediatric patients have not been established. Treatment experience with rosuvastatin in a pediatric population is limited to 8 patients with homozygous FH. None of these patients was below 8 years of age.

Geriatric Use

Of the 10,275 patients in clinical studies with rosuvastatin, 3,159 (31%) were 65 years and older, and 698 (6.8%) were 75 years and older. The overall frequency of adverse events and types of adverse events were similar in patients above and below 65 years of age. (See WARNINGS, Myopathy/Rhabdomyolysis.)

The efficacy of rosuvastatin in the geriatric population (≥65 years of age) was comparable to the efficacy observed in the non-elderly.

ADVERSE REACTIONS

Rosuvastatin is generally well tolerated. Adverse reactions have usually been mild and transient. In clinical studies of 10,275 patients, 3.7% were discontinued due to adverse experiences attributable to rosuvastatin. The most frequent adverse events thought to be related to rosuvastatin were myalgia, constipation, asthenia, abdominal pain, and nausea.

Clinical Adverse Experiences

Adverse experiences, regardless of causality assessment, reported in ≥2% of patients in placebo-controlled clinical studies of rosuvastatin are shown in Table 6; discontinuations due to adverse events in these studies of up to 12 weeks duration occurred in 3% of patients on rosuvastatin and 5% on placebo.

Table 6. Adverse Events in Placebo-Controlled Studies

Adverse Event	Rosuvastatin N=744	Placebo N=382
Pharyngitis	9.0	7.6
Headache	5.5	5.0
Diarrhea	3.4	2.9
Dyspepsia	3.4	3.1
Nausea	3.4	3.1
Myalgia	2.8	1.3
Asthenia	2.7	2.6
Back Pain	2.6	2.4
Flu syndrome	2.3	1.8
Urinary tract infection	2.3	1.6
Rhinitis	2.2	2.1
Sinusitis	2.0	1.8

In addition, the following adverse events were reported, regardless of causality assessment, in ≥1% of 10,275 patients treated with rosuvastatin in clinical studies. The events in *italics* occurred in ≥2% of these patients.

Body as a Whole: *Abdominal pain, accidental injury, chest pain, infection, pain*, pelvic pain, and neck pain.

Cardiovascular System: *Hypertension*, angina pectoris, vasodilatation, and palpitation.

Digestive System: *Constipation, gastroenteritis*, vomiting, flatulence, periodontal abscess, and gastritis.

Endocrine: Diabetes mellitus.

Hemic and Lymphatic System: Anemia and ecchymosis.

Metabolic and Nutritional Disorders: *Peripheral edema.*

Musculoskeletal System: *Arthritis, arthralgia*, and pathological fracture.

Nervous System: *Dizziness, insomnia, hypertonia, paresthesia, depression*, anxiety, vertigo and neuralgia.

Respiratory System: *Bronchitis, cough increased*, dyspnea, pneumonia, and asthma.

Skin and Appendages: *Rash* and pruritus.

Laboratory Abnormalities: In the rosuvastatin clinical trial program, dipstick-positive proteinuria and microscopic hematuria were observed among rosuvastatin-treated patients, predominantly in patients dosed above the recommended dose range (i.e., 80 mg). However, this finding was more frequent in patients taking rosuvastatin 40 mg, when compared to lower doses of rosuvastatin or comparator statins, though it was generally transient and was not associated with worsening renal function. (See PRECAUTIONS, Laboratory Tests.)

Other abnormal laboratory values reported were elevated creatine phosphokinase, transaminases, hyperglycemia, glutamyl transpeptidase, alkaline phosphatase, bilirubin, and thyroid function abnormalities.

Other adverse events reported less frequently than 1% in the rosuvastatin clinical study program, regardless of causality assessment, included arrhythmia, hepatitis, hypersensitivity reactions (i.e., face edema, thrombocytopenia, leukopenia, vesiculobullous rash, urticaria, and angioedema), kidney failure, syncope, myasthenia, myositis, pancreatitis, photosensitivity reaction, myopathy, and rhabdomyolysis.

Postmarketing Experience

In addition to the events reported above, as with other drugs in this class, the following event has been reported during postmarketing experience with CRESTOR, regardless of causality assessment: very rare cases of jaundice.

OVERDOSAGE

There is no specific treatment in the event of overdose. In the event of overdose, the patient should be treated symptomatically and supportive measures instituted as required. Hemodialysis does not significantly enhance clearance of rosuvastatin.

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving CRESTOR and should continue on this diet during treatment. CRESTOR can be administered as a single dose at any time of day, with or without food.

Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Type IIa and IIb)

The dose range for CRESTOR is 5 to 40 mg once daily. Therapy with CRESTOR should be individualized according to goal of therapy and response. The usual recommended starting dose of CRESTOR is 10 mg once daily. However, initiation of therapy with 5 mg once daily should be considered for patients requiring less aggressive LDL-C reductions, who have predisposing factors for myopathy, and as noted below for special populations such as patients taking cyclosporine, Asian patients, and patients with severe renal insufficiency (see CLINICAL PHARMACOLOGY, Race, and Renal Insufficiency, and Drug Interactions). For patients with marked hypercholesterolemia (LDL-C > 190 mg/dL) and aggressive lipid targets, a 20-mg starting dose may be considered. After initiation and/or upon titration of CRESTOR, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly.

The 40-mg dose of CRESTOR is reserved only for those patients who have not achieved their LDL-C goal utilizing the 20 mg dose of CRESTOR once daily (see WARNINGS, Myopathy/Rhabdomyolysis). When initiating statin therapy or switching from another statin therapy, the appropriate CRESTOR starting dose should first be utilized, and only then titrated according to the patient's individualized goal of therapy.

Homozygous Familial Hypercholesterolemia

The recommended starting dose of CRESTOR is 20 mg once daily in patients with homozygous FH. The maximum recommended daily dose is 40 mg. CRESTOR should be used in these patients as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable. Response to therapy should be estimated from pre-apheresis LDL-C levels.

Dosage in Asian Patients

Initiation of CRESTOR therapy with 5 mg once daily should be considered for Asian patients. The potential for increased systemic exposures relative to Caucasians is relevant when considering escalation of dose in cases where hypercholesterolemia is not adequately controlled at doses of 5, 10, or 20 mg once daily (see WARNINGS, Myopathy/Rhabdomyolysis, CLINICAL PHARMACOLOGY, Special Populations, Race, and PRECAUTIONS, General).

Dosage in Patients Taking Cyclosporine

In patients taking cyclosporine, therapy should be limited to CRESTOR 5 mg once daily (see WARNINGS Myopathy/Rhabdomyolysis, and PRECAUTIONS, Drug Interactions).

Concomitant Lipid-Lowering Therapy

The effect of CRESTOR on LDL-C and total-C may be enhanced when used in combination with a bile acid binding resin. If CRESTOR is used in combination with gemfibrozil, the dose of CRESTOR should be limited to 10 mg once daily (see WARNINGS, Myopathy/Rhabdomyolysis, and PRECAUTIONS, Drug Interactions).

Dosage in Patients With Renal Insufficiency

No modification of dosage is necessary for patients with mild to moderate renal insufficiency. For patients with severe renal impairment (CL_{cr} <30 mL/min/1.73 m^2) not on hemodialysis, dosing of CRESTOR should be started at 5 mg once daily and not to exceed 10 mg once daily (see PRECAUTIONS, General, and CLINICAL PHARMACOLOGY, Special Populations, Renal Insufficiency).

HOW SUPPLIED

CRESTOR® (rosuvastatin calcium) Tablets are supplied as:

5 mg tablets: Yellow, round, biconvex, coated tablets identified as "CRESTOR" and "5" debossed on one side and plain on the other side of the tablet.
(NDC 0310-0755-90) bottles of 90

10 mg tablets: Pink, round, biconvex, coated tablets identified as "CRESTOR" and "10" debossed on one side and plain on the other side of the tablet.
(NDC 0310-0751-90) bottles of 90
(NDC 0310-0751-39) unit dose packages of 100

20 mg tablets: Pink, round, biconvex, coated tablets identified as "CRESTOR" and "20" debossed on one side and plain on the other side of the tablet.
(NDC 0310-0752-90) bottles of 90
(NDC 0310-0752-39) unit dose packages of 100

40 mg tablets: Pink, oval, biconvex, coated tablets identified as "CRESTOR" debossed on one side and "40" debossed on the other side of the tablet.
(NDC 0310-0754-30) bottles of 30
(NDC 0310-0754-39) unit dose packages of 100

Storage

Store at controlled room temperature, 20–25°C (68–77°F) [see USP]. Protect from moisture.

Rx only

Licensed from SHIONOGI & CO., LTD., Osaka, Japan

Manufactured for:
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850
By: IPR Pharmaceuticals, Inc.
Carolina, PR 00984
630301
Rev. 03/05

Shown in Product Identification Guide, page 306

Continued on next page

the CURE trial, the incidence of peptic, gastric or duodenal ulcers was 0.4% for PLAVIX (clopidogrel bisulfate) + aspirin and 0.3% for placebo + aspirin.

Cases of diarrhea were reported in the CAPRIE trial in 4.5% of patients in the PLAVIX group compared to 3.4% in the aspirin group. However, these were rarely severe (PLAVIX=0.2% and aspirin=0.1%). In the CURE trial, the incidence of diarrhea for patients receiving PLAVIX + aspirin was 2.1% compared to 2.2% for those receiving placebo + aspirin.

In the CAPRIE trial, the incidence of patients withdrawing from treatment because of gastrointestinal adverse reactions was 3.2% for PLAVIX and 4.0% for aspirin. In the CURE trial, the incidence of patients withdrawing from treatment because of gastrointestinal adverse reactions was 0.9% for PLAVIX + aspirin compared with 0.8% for placebo + aspirin.

Rash and Other Skin Disorders: In the CAPRIE trial, the incidence of skin and appendage disorders in patients receiving PLAVIX was 15.8% (0.7% serious); the corresponding rate in aspirin patients was 13.1% (0.5% serious). In the CURE trial, the incidence of rash or other skin disorders in patients receiving PLAVIX + aspirin was 4.0% compared to 3.5% for those receiving placebo + aspirin.

In the CAPRIE trial, the overall incidence of patients withdrawing from treatment because of skin and appendage disorders adverse reactions was 1.5% for PLAVIX and 0.8% for aspirin. In the CURE trial, the incidence of patients withdrawing because of skin and appendage disorders adverse reactions was 0.7% for PLAVIX + aspirin compared with 0.3% for placebo + aspirin.

Adverse events occurring in ≥2.5% of patients on PLAVIX (clopidogrel bisulfate) in the CAPRIE controlled clinical trial are shown below regardless of relationship to PLAVIX. The median duration of therapy was 20 months, with a maximum of 3 years.

Table 4: Adverse Events Occurring in ≥2.5% of PLAVIX Patients in CAPRIE

Body System / Event	% Incidence (% Discontinuation) PLAVIX [n=9599]		Aspirin [n=9586]	
Body as a Whole - general disorders				
Chest Pain	8.3	(0.2)	8.3	(0.3)
Accidental/Inflicted Injury	7.9	(0.1)	7.3	(0.1)
Influenza-like symptoms	7.5	(<0.1)	7.0	(<0.1)
Pain	6.4	(0.1)	6.3	(0.1)
Fatigue	3.3	(0.1)	3.4	(0.1)
Cardiovascular disorders, general				
Edema	4.1	(<0.1)	4.5	(<0.1)
Hypertension	4.3	(<0.1)	5.1	(<0.1)
Central & peripheral nervous system disorders				
Headache	7.6	(0.3)	7.2	(0.2)
Dizziness	6.2	(0.2)	6.7	(0.3)
Gastrointestinal system disorders				
Abdominal pain	5.6	(0.7)	7.1	(1.0)
Dyspepsia	5.2	(0.6)	6.1	(0.7)
Diarrhea	4.5	(0.4)	3.4	(0.3)
Nausea	3.4	(0.5)	3.8	(0.4)
Metabolic & nutritional disorders				
Hypercholesterolemia	4.0	(0)	4.4	(<0.1)
Musculo-skeletal system disorders				
Arthralgia	6.3	(0.1)	6.2	(0.1)
Back Pain	5.8	(0.1)	5.3	(<0.1)
Platelet, bleeding, & clotting disorders				
Purpura/Bruise	5.3	(0.3)	3.7	(0.1)
Epistaxis	2.9	(0.2)	2.5	(0.1)
Psychiatric disorders				
Depression	3.6	(0.1)	3.9	(0.2)
Respiratory system disorders				
Upper resp tract infection	8.7	(<0.1)	8.3	(<0.1)
Dyspnea	4.5	(0.1)	4.7	(0.1)
Rhinitis	4.2	(0.1)	4.2	(<0.1)
Bronchitis	3.7	(0.1)	3.7	(0)
Coughing	3.1	(<0.1)	2.7	(<0.1)
Skin & appendage disorders				
Rash	4.2	(0.5)	3.5	(0.2)
Pruritus	3.3	(0.3)	1.6	(0.1)
Urinary system disorders				
Urinary tract infection	3.1	(0)	3.5	(0.1)

Incidence of discontinuation, regardless of relationship to therapy, is shown in parentheses.

Adverse events occurring in ≥2.0% of patients on PLAVIX (clopidogrel bisulfate) in the CURE controlled clinical trial are shown below regardless of relationship to PLAVIX.

Table 5: Adverse Events Occurring in ≥2.0% of PLAVIX Patients in CURE

Body System / Event	% Incidence (% Discontinuation) PLAVIX (+ aspirin)* [n=6259]		Placebo (+ aspirin)* [n=6303]	
Body as a Whole - general disorders				
Chest Pain	2.7	(<0.1)	2.8	(0.0)
Central & peripheral nervous system disorders				
Headache	3.1	(0.1)	3.2	(0.1)
Dizziness	2.4	(0.1)	2.0	(<0.1)
Gastrointestinal system disorders				
Abdominal pain	2.3	(0.3)	2.8	(0.3)
Dyspepsia	2.0	(0.1)	1.9	(<0.1)
Diarrhea	2.1	(0.1)	2.2	(0.1)

*Other standard therapies were used as appropriate.

Other adverse experiences of potential importance occurring in 1% to 2.5% of patients receiving PLAVIX (clopidogrel bisulfate) in the CAPRIE or CURE controlled clinical trials are listed below regardless of relationship to PLAVIX. In general, the incidence of these events was similar to that in patients receiving aspirin (in CAPRIE) or placebo + aspirin (in CURE).

Autonomic Nervous System Disorders: Syncope, Palpitation. *Body as a Whole - general disorders:* Asthenia, Fever, Hernia. *Cardiovascular disorders:* Cardiac failure. *Central and peripheral nervous system disorders:* Cramps legs, Hypoaesthesia, Neuralgia, Paraesthesia, Vertigo. *Gastrointestinal system disorders:* Constipation, Vomiting. *Heart rate and rhythm disorders:* Fibrillation atrial. *Liver and biliary system disorders:* Hepatic enzymes increased. *Metabolic and nutritional disorders:* Gout, hyperuricemia, non-protein nitrogen (NPN) increased. *Musculo-skeletal system disorders:* Arthritis, Arthrosis. *Platelet, bleeding & clotting disorders:* GI hemorrhage, hematoma, platelets decreased. *Psychiatric disorders:* Anxiety, Insomnia. *Red blood cell disorders:* Anemia. *Respiratory system disorders:* Pneumonia, Sinusitis. *Skin and appendage disorders:* Eczema, Skin ulceration. *Urinary system disorders:* Cystitis. *Vision disorders:* Cataract, Conjunctivitis.

Other potentially serious adverse events which may be of clinical interest but were rarely reported (<1%) in patients who received PLAVIX in the CAPRIE or CURE controlled clinical trials are listed below regardless of relationship to PLAVIX. In general, the incidence of these events was similar to that in patients receiving aspirin (in CAPRIE) or placebo + aspirin (in CURE).

Body as a whole: Allergic reaction, necrosis ischemic. *Cardiovascular disorders:* Edema generalized. *Gastrointestinal system disorders:* Gastric ulcer perforated, gastritis hemorrhagic, upper GI ulcer hemorrhagic. *Liver and Biliary system disorders:* Bilirubinemia, hepatitis infectious, liver fatty. *Platelet, bleeding and clotting disorders:* hemarthrosis, hematuria, hemoptysis, hemorrhage intracranial, hemorrhage retroperitoneal, hemorrhage of operative wound, ocular hemorrhage, pulmonary hemorrhage, purpura allergic, thrombocytopenia. *Red blood cell disorders:* Anemia aplastic, anemia hypochromic. *Reproductive disorders, female:* Menorrhagia. *Respiratory system disorders:* Hemothorax. *Skin and appendage disorders:* Bullous eruption, rash erythematous, rash maculopapular, urticaria. *Urinary system disorders:* Abnormal renal function, acute renal failure. *White cell and reticuloendothelial system disorders:* Agranulocytosis, granulocytopenia, leukemia, leukopenia, neutrophils decreased.

Postmarketing Experience

The following events have been reported spontaneously from worldwide postmarketing experience:

- *Body as a whole:*
  - — hypersensitivity reactions, anaphylactoid reactions, serum sickness
- *Central and Peripheral Nervous System disorders:*
  - — confusion, hallucinations, taste disorders
- *Hepato-biliary disorders:*
  - — abnormal liver function test, hepatitis (non-infectious), acute liver failure
- *Platelet, Bleeding and Clotting disorders:*
  - — cases of bleeding with fatal outcome (especially intracranial, gastrointestinal and retroperitoneal hemorrhage)
  - — agranulocytosis, aplastic anemia/pancytopenia, thrombotic thrombocytopenic purpura (TTP) — some cases with fatal outcome (see **WARNINGS**).
  - — conjunctival, ocular and retinal bleeding
- *Respiratory, thoracic and mediastinal disorders:*
  - — bronchospasm, interstitial pneumonitis
- *Skin and subcutaneous tissue disorders:*
  - — angioedema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, lichen planus
- *Renal and urinary disorders:*
  - — glomerulopathy, increased creatinine levels
- *Vascular disorders:*
  - — vasculitis, hypotension
- *Gastrointestinal disorders:*
  - — colitis (including ulcerative or lymphocytic colitis), pancreatitis, stomatitis
- *Musculoskeletal, connective tissue and bone disorders:*
  - — myalgia

OVERDOSAGE

Overdose following clopidogrel administration may lead to prolonged bleeding time and subsequent bleeding complications. A single oral dose of clopidogrel at 1500 or 2000 mg/kg was lethal to mice and to rats and at 3000 mg/kg to baboons. Symptoms of acute toxicity were vomiting (in baboons), prostration, difficult breathing, and gastrointestinal hemorrhage in all species.

Recommendations About Specific Treatment:

Based on biological plausibility, platelet transfusion may be appropriate to reverse the pharmacological effects of PLAVIX (clopidogrel bisulfate) if quick reversal is required.

DOSAGE AND ADMINISTRATION

Recent MI, Recent Stroke, or Established Peripheral Arterial Disease

The recommended daily dose of PLAVIX is 75 mg once daily.

Acute Coronary Syndrome

For patients with acute coronary syndrome (unstable angina/non-Q-wave MI), PLAVIX should be initiated with a single 300 mg loading dose and then continued at 75 mg once daily. Aspirin (75 mg-325 mg once daily) should be initiated and continued in combination with PLAVIX. In CURE, most patients with Acute Coronary Syndrome also received heparin acutely (see **CLINICAL STUDIES**).

PLAVIX can be administered with or without food.

No dosage adjustment is necessary for elderly patients or patients with renal disease. (See **Clinical Pharmacology: Special Populations.**)

HOW SUPPLIED

PLAVIX (clopidogrel bisulfate) is available as a pink, round, biconvex, film-coated tablet debossed with "75" on one side and "1171" on the other. Tablets are provided as follows:

NDC 63653-1171-6 bottles of 30
NDC 63653-1171-1 bottles of 90
NDC 63653-1171-5 bottles of 500
NDC 63653-1171-3 blisters of 100

Storage

Store at 25° C (77° F); excursions permitted to 15°–30° C (59°–86° F) [See USP Controlled Room Temperature].

Distributed by:
Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership
New York, NY 10016
sanofi~synthelabo
Bristol-Myers Squibb Company

PLAVIX® is a registered trademark of Sanofi-Synthelabo

Revised: May 2005

Shown in Product Identification Guide, page 309 ℞

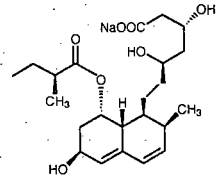
PRAVACHOL® ℞

[*pră-vă-kŏl*]
(pravastatin sodium) Tablets
Rx only

DESCRIPTION

PRAVACHOL® (pravastatin sodium) is one of a class of lipid-lowering compounds, the HMG-CoA reductase inhibitors, which reduce cholesterol biosynthesis. These agents are competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme catalyzing the early rate-limiting step in cholesterol biosynthesis, conversion of HMG-CoA to mevalonate.

Pravastatin sodium is designated chemically as 1-Naphthalene-heptanoic acid, 1,2,6,7,8,8a-hexahydro-β,δ,6-trihydroxy-2-methyl-8-(2-methyl-1-oxobutoxy)-, monosodium salt, [1S-[1α(βS*,δS*),2α,6α,8β(R*),8aα]]-. Structural formula:



$C_{23}H_{35}NaO_7$ MW 446.52

Pravastatin sodium is an odorless, white to off-white, fine or crystalline powder. It is a relatively polar hydrophilic compound with a partition coefficient (octanol/water) of 0.59 at a pH of 7.0. It is soluble in methanol and water (>300 mg/mL), slightly soluble in isopropanol, and practically insoluble in acetone, acetonitrile, chloroform, and ether.

PRAVACHOL is available for oral administration as 10 mg, 20 mg, 40 mg, and 80 mg tablets. Inactive ingredients include: croscarmellose sodium, lactose, magnesium oxide, magnesium stearate, microcrystalline cellulose, and povidone. The 10 mg tablet also contains Red Ferric Oxide, the 20 mg and 80 mg tablets also contain Yellow Ferric Oxide, and the 40 mg tablet also contains Green Lake Blend (mixture of D&C Yellow No. 10-Aluminum Lake and FD&C Blue No. 1-Aluminum Lake).

Continued on next page

Pravachol—Cont.

CLINICAL PHARMACOLOGY

Cholesterol and triglycerides in the bloodstream circulate as part of lipoprotein complexes. These complexes can be separated by density ultracentrifugation into high (HDL), intermediate (IDL), low (LDL), and very low (VLDL) density lipoprotein fractions. Triglycerides (TG) and cholesterol synthesized in the liver are incorporated into very low density lipoproteins (VLDLs) and released into the plasma for delivery to peripheral tissues. In a series of subsequent steps, VLDLs are transformed into intermediate density lipoproteins (IDLs), and cholesterol-rich low density lipoproteins (LDLs). High density lipoproteins (HDLs), containing apolipoprotein A, are hypothesized to participate in the reverse transport of cholesterol from tissues back to the liver.

PRAVACHOL (pravastatin sodium) produces its lipid-lowering effect in two ways. First, as a consequence of its reversible inhibition of HMG-CoA reductase activity, it effects modest reductions in intracellular pools of cholesterol. This results in an increase in the number of LDL-receptors on cell surfaces and enhanced receptor-mediated catabolism and clearance of circulating LDL. Second, pravastatin inhibits LDL production by inhibiting hepatic synthesis of VLDL, the LDL precursor.

Clinical and pathologic studies have shown that elevated levels of total cholesterol (Total-C), low density lipoprotein cholesterol (LDL-C), and apolipoprotein B (Apo B - a membrane transport complex for LDL) promote human atherosclerosis. Similarly, decreased levels of HDL-cholesterol (HDL-C) and its transport complex, apolipoprotein A, are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of Total-C and LDL-C and inversely with the level of HDL-C. Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, IDL, and remnants, can also promote atherosclerosis. Elevated plasma TG are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

In both normal volunteers and patients with hypercholesterolemia, treatment with PRAVACHOL reduced Total-C, LDL-C, and apolipoprotein B. PRAVACHOL also reduced VLDL-C and TG and produced increases in HDL-C and apolipoprotein A. The effects of pravastatin on Lp (a), fibrinogen, and certain other independent biochemical risk markers for coronary heart disease are unknown. Although pravastatin is relatively more hydrophilic than other HMG-CoA reductase inhibitors, the effect of relative hydrophilicity, if any, on either efficacy or safety has not been established.

In one primary (West of Scotland Coronary Prevention Study – WOS)[1] and two secondary (Long-term Intervention with Pravastatin in Ischemic Disease – LIPID[2] and the Cholesterol and Recurrent Events – CARE[3]) prevention studies, PRAVACHOL has been shown to reduce cardiovascular morbidity and mortality across a wide range of cholesterol levels (see **Clinical Studies**).

Pharmacokinetics/Metabolism

PRAVACHOL is administered orally in the active form. In clinical pharmacology studies in man, pravastatin is rapidly absorbed, with peak plasma levels of parent compound attained 1 to 1.5 hours following ingestion. Based on urinary recovery of radiolabeled drug, the average oral absorption of pravastatin is 34% and absolute bioavailability is 17%. While the presence of food in the gastrointestinal tract reduces systemic bioavailability, the lipid-lowering effects of the drug are similar whether taken with, or 1 hour prior, to meals.

Pravastatin undergoes extensive first-pass extraction in the liver (extraction ratio 0.66), which is its primary site of action, and the primary site of cholesterol synthesis and of LDL-C clearance. *In vitro* studies demonstrated that pravastatin is transported into hepatocytes with substantially less uptake into other cells. In view of pravastatin's apparently extensive first-pass hepatic metabolism, plasma levels may not necessarily correlate perfectly with lipid-lowering efficacy. Pravastatin plasma concentrations [including: area under the concentration-time curve (AUC), peak (C_{max}), and steady-state minimum (C_{min})] are directly proportional to administered dose. Systemic bioavailability of pravastatin administered following a bedtime dose was decreased 60% compared to that following an AM dose. Despite this decrease in systemic bioavailability, the efficacy of pravastatin administered once daily in the evening, although not statistically significant, was marginally more effective than that after a morning dose. This finding of lower systemic bioavailability suggests greater hepatic extraction of the drug following the evening dose. Steady-state AUCs, C_{max} and C_{min} plasma concentrations showed no evidence of pravastatin accumulation following once or twice daily administration of PRAVACHOL (pravastatin sodium) tablets. Approximately 50% of the circulating drug is bound to plasma proteins. Following single dose administration of ^{14}C-pravastatin, the elimination half-life (t½) for total radioactivity (pravastatin plus metabolites) in humans is 77 hours. Pravastatin, like other HMG-CoA reductase inhibitors, has variable bioavailability. The coefficient of variation (CV), based on between-subject variability, was 50% to 60% for AUC. Pravastatin 20 mg was administered under fasting conditions in adults. The geometric means of C_{max} and AUC ranged from 23.3 to 26.3 ng/mL and from 54.7 to 62.2 ng*hr/mL, respectively.

Approximately 20% of a radiolabeled oral dose is excreted in urine and 70% in the feces. After intravenous administration of radiolabeled pravastatin to normal volunteers, approximately 47% of total body clearance was via renal excretion and 53% by non-renal routes (i.e., biliary excretion and biotransformation). Since there are dual routes of elimination, the potential exists both for compensatory excretion by the alternate route as well as for accumulation of drug and/or metabolites in patients with renal or hepatic insufficiency.

In a study comparing the kinetics of pravastatin in patients with biopsy confirmed cirrhosis (N=7) and normal subjects (N=7), the mean AUC varied 18-fold in cirrhotic patients and 5-fold in healthy subjects. Similarly, the peak pravastatin values varied 47-fold for cirrhotic patients compared to 6-fold for healthy subjects.

Biotransformation pathways elucidated for pravastatin include: (a) isomerization to 6-epi pravastatin and the 3α-hydroxyisomer of pravastatin (SQ 31,906), (b) enzymatic ring hydroxylation to SQ 31,945, (c) ω-1 oxidation of the ester side chain, (d) β-oxidation of the carboxy side chain, (e) ring oxidation followed by aromatization, (f) oxidation of a hydroxyl group to a keto group, and (g) conjugation. The major degradation product is the 3α-hydroxy isomeric metabolite, which has one-tenth to one-fortieth the HMG-CoA reductase inhibitory activity of the parent compound.

In a single oral dose study using pravastatin 20 mg, the mean AUC for pravastatin was approximately 27% greater and the mean cumulative urinary excretion (CUE) approximately 19% lower in elderly men (65 to 75 years old) compared with younger men (19 to 31 years old). In a similar study conducted in women, the mean AUC for pravastatin was approximately 46% higher and the mean CUE approximately 18% lower in elderly women (65 to 78 years old) compared with younger women (18 to 38 years old). In both studies, C_{max}, T_{max} and t½ values were similar in older and younger subjects.

After two weeks of once-daily 20 mg oral pravastatin administration, the geometric means of AUC were 80.7 (CV 44%) and 44.8 (CV 89%) ng*hr/mL for children (8-11 years, n=14) and adolescents (12-16 years, n=10), respectively. The corresponding values for C_{max} were 42.4 (CV 54%) and 18.6 ng/mL (CV 100%) for children and adolescents, respectively. No conclusion can be made based on these findings due to the small number of samples and large variability.

Clinical Studies

Prevention of Coronary Heart Disease

In the Pravastatin Primary Prevention Study (West of Scotland Coronary Prevention Study – WOS),[1] the effect of PRAVACHOL (pravastatin sodium) on fatal and nonfatal coronary heart disease (CHD) was assessed in 6595 men 45-64 years of age, without a previous myocardial infarction (MI), and with LDL-C levels between 156-254 mg/dL (4-6.7 mmol/L). In this randomized, double-blind, placebo-controlled study, patients were treated with standard care, including dietary advice, and either PRAVACHOL 40 mg daily (N=3302) or placebo (N=3293) and followed for a median duration of 4.8 years. Median (25th, 75th percentile) percent changes from baseline after 6 months of pravastatin treatment in Total C, LDL-C, TG, and HDL were -20.3 (-26.9, -11.7), -27.7 (-36.0, -16.9), -9.1 (-27.6, 12.5), and 6.7 (-2.1, 15.6), respectively.

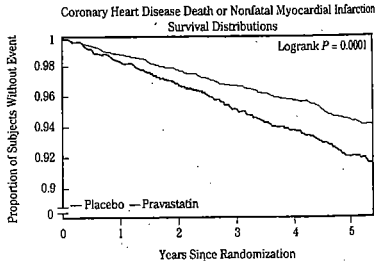
PRAVACHOL significantly reduced the rate of first coronary events (either coronary heart disease [CHD] death or nonfatal MI) by 31% [248 events in the placebo group (CHD death=44, nonfatal MI=204) vs 174 events in the PRAVACHOL group (CHD death=31, nonfatal MI=143), p=0.0001 (see figure below)]. The risk reduction with PRAVACHOL was similar and significant throughout the entire range of baseline LDL cholesterol levels. This reduction was also similar and significant across the age range studied with a 40% risk reduction for patients younger than 55 years and a 27% risk reduction for patients 55 years and older. The Pravastatin Primary Prevention Study included only men and therefore it is not clear to what extent these data can be extrapolated to a similar population of female patients.

[See figure at top of next column]

PRAVACHOL also significantly decreased the risk for undergoing myocardial revascularization procedures (coronary artery bypass graft [CABG] surgery or percutaneous transluminal coronary angioplasty [PTCA]) by 37% (80 vs 51 patients, p=0.009) and coronary angiography by 31% (128 vs 90, p=0.007). Cardiovascular deaths were decreased by 32% (73 vs 50, p=0.03) and there was no increase in death from non-cardiovascular causes.

Table 1: LIPID – Primary and Secondary Endpoints

Event	Number (%) of Subjects: Pravastatin 40 mg (N=4512)	Placebo (N=4502)	Risk Reduction	*P*-value
Primary Endpoint				
CHD mortality	287 (6.4)	373 (8.3)	24%	0.0004
Secondary Endpoints				
Total mortality	498 (11.0)	633 (14.1)	23%	<0.0001
CHD mortality or non-fatal MI	557 (12.3)	715 (15.9)	24%	<0.0001
Myocardial revascularization procedures (CABG or PTCA)	584 (12.9)	706 (15.7)	20%	<0.0001
Stroke				
All-cause	169 (3.7)	204 (4.5)	19%	0.0477
Non-hemorrhagic	154 (3.4)	196 (4.4)	23%	0.0154
Cardiovascular mortality	331 (7.3)	433 (9.6)	25%	<0.0001



Secondary Prevention of Cardiovascular Events

In the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID)[2] study, the effect of PRAVACHOL (pravastatin sodium), 40 mg daily, was assessed in 9014 patients (7498 men; 1516 women; 3514 elderly patients [age ≥65 years]; 782 diabetic patients) who had experienced either an MI (5754 patients) or had been hospitalized for unstable angina pectoris (3260 patients) in the preceding 3-36 months. Patients in this multicenter, double-blind, placebo-controlled study participated for an average of 5.6 years (median of 5.9 years) and at randomization had total cholesterol between 114 and 563 mg/dL (mean 219 mg/dL), LDL-C between 46 and 274 mg/dL (mean 150 mg/dL), triglycerides between 35 and 271 mg/dL (mean 160 mg/dL), and HDL-C between 1 and 103 mg/dL (mean 37 mg/dL). At baseline, 82% of patients were receiving aspirin and 76% were receiving antihypertensive medication. Treatment with PRAVACHOL significantly reduced the risk for total mortality by reducing coronary death (see **Table 1**). The risk reduction due to treatment with PRAVACHOL on CHD mortality was consistent regardless of age. PRAVACHOL significantly reduced the risk for total mortality (by reducing CHD death) and CHD events (CHD mortality or nonfatal MI) in patients who qualified with a history of either MI or hospitalization for unstable angina pectoris.

[See table 1 above]

In the Cholesterol and Recurrent Events (CARE)[3] study, the effect of PRAVACHOL, 40 mg daily, on coronary heart disease death and nonfatal MI was assessed in 4159 patients (3583 men and 576 women) who had experienced a myocardial infarction in the preceding 3-20 months and who had normal (below the 75th percentile of the general population) plasma total cholesterol levels. Patients in this double-blind, placebo controlled study participated for an average of 4.9 years and had a mean baseline total cholesterol of 209 mg/dL. LDL cholesterol levels in this patient population ranged from 101 mg/dL-180 mg/dL (mean=139 mg/dL). At baseline, 84% of patients were receiving aspirin and 82% were taking antihypertensive medications. Median (25th, 75th percentile) percent changes from baseline after 6 months of pravastatin treatment in Total C, LDL-C, TG, and HDL were -22.0 (-28.4, -14.9), -32.4 (-39.9, -23.7), -11.0 (-26.5, 8.6); and 5.1 (-2.9, 12.7), respectively. Treatment with PRAVACHOL significantly reduced the rate of first recurrent coronary events (either CHD death or nonfatal MI), the risk of undergoing revascularization procedures (PTCA, CABG), and the risk for stroke or transient ischemic attack (TIA) (see **Table 2**).

[See table 2 at top of next page]

In the Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC I)[4] study, the effect of pravastatin therapy on coronary atherosclerosis was assessed by coronary angiography in patients with coronary disease and moderate hypercholesterolemia (baseline LDL-C range= 130-190 mg/dL). In this double-blind, multicenter, controlled clinical trial, angiograms were evaluated at baseline and at three years in 264 patients. Although the difference between pravastatin and placebo for the primary endpoint (per-patient change in mean coronary artery diameter) and one of two secondary endpoints (change in percent lumen diameter stenosis) did not reach statistical significance, for the secondary endpoint of change in minimum lumen diameter, statistically significant slowing of disease was seen in the pravastatin treatment group (p=0.02).

In the Regression Growth Evaluation Statin Study (REGRESS)[5], the effect of pravastatin on coronary atherosclerosis was assessed by coronary angiography in 885 patients with angina pectoris, angiographically documented coronary artery disease and hypercholesterolemia (baseline

total cholesterol range= blind, multicenter, contro evaluated at baseline an treated with pravastatin sclerosis was significant as assessed by chang (p=0.037) and minimum Analysis of pooled even Lipids and Atherosclero II)[5], REGRESS, and the Study (KAPS)[7] (combin with pravastatin was as cant reduction in the co fatal myocardial infarc versus 21 events or 2.4% dominant effect of prav fatal myocardial infarc *Primary Hypercholeste IIb)*

PRAVACHOL (pravast ducing Total-C, LDL-C with heterozygous fa and non-familial (non- olemia, and mixed dy seen within 1 week, a achieved within 4 wee ing extended periods is effective in reducin hypercholesterolemic myocardial infarction. A single daily dose is dose given twice a placebo-controlled stu cholesterolemia, treat ranging from 10 mg t decreased Total-C, I LDL-C/HDL-C ratios In a pooled analysis placebo-controlled st cholesterolemia, trea of 80 mg (N=277) si and TG. The 25th an in LDL-C for pravas efficacy results of t with the pooled data Treatment with PRA and PRAVACHOL creases in HDL-C (s

Table 3: Primary H Dose One

Dose	Mean Percent Cl
Placebo (N=36)	
10 mg (N=18)	
20 mg (N=19)	
40 mg (N=18)	
	Mean Percent Cl
Placebo (N=162)	
80 mg (N=277)	

*a multicenter, d
**pooled analysis controlled studi

In another clinica in combination w taking cholestyra equal to or greate astatin attenuat TG levels (whic significance).

Hypertriglyceride

The response to perlipidemia (b <160 mg/dL) wa the Cholesterol pravastatin-trea line triglyceride Table 4).

Table 4: Pati Hyperlipi Pe

Triglycerides
Total-C
LDL-C
HDL-C
Non-HDL-C

Dysbetalipopro

The response studies of 46 p Type III dysbe

K REFERENCE®

P-value

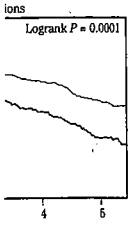
0.0004

<0.0001
<0.0001

<0.0001

0.0477
0.0154
<0.0001

ıtal Myocardial Infarction
ions



nization

ere decreased by 32%
ıcrease in death from

ar Events
ravastatin in Ischemic
PRAVACHOL (prava-
ssed in 9014 patients
ly patients [age ≥65
experienced either an
alized for unstable an-
eceding 3-36 months.
uble-blind, placebo-
average of 5.6 years
ization had total cho-
L (mean 219 mg/dL),
ıean 150 mg/dL), trig-
L (mean 160 mg/dL),
(mean 37 mg/dL). At
ving aspirin and 76%
edication. Treatment
ıced the risk for total
(see **Table 1**). The risk
/ACHOL on CHD mor-
. PRAVACHOL signif-
ıortality (by reducing
mortality or nonfatal
history of either MI or
ectoris.

nts (CARE)[3] study, the
on coronary heart dis-
essed in 4159 patients
experienced a myocar-
months and who had
he general population)
tients in this double-
cipated for an average
ne total cholesterol of
this patient population
(mean=139 mg/dL). At
iving aspirin and 82%
cations. Median (25th,
from baseline after 6
Total C, LDL-C, TG,
)2.4 (-39.9, -23.7), -11.0
ctively. Treatment with
the rate of first recur-
ath or nonfatal MI), the
on procedures (PTCA,
ansient ischemic attack

ıerosclerosis in the Cor-
ıe effect of pravastatin
s was assessed by coro-
ı coronary disease and
aseline LDL-C range=
lind, multicenter, con-
re evaluated at baseline
Although the difference
ır the primary endpoint
ry artery diameter) and
ıange in percent lumen
ıtistical significance, for
ı minimum lumen diam-
g of disease was seen in
=0.02).
ıluation Statin Study
ıtin on coronary athero-
angiography in 885 pa-
graphically documented
holesterolemia (baseline

total cholesterol range=160-310 mg/dL). In this double-blind, multicenter, controlled clinical trial, angiograms were evaluated at baseline and at two years in 653 patients (323 treated with pravastatin). Progression of coronary atherosclerosis was significantly slowed in the pravastatin group as assessed by changes in mean segment diameter (p=0.037) and minimum obstruction diameter (p=0.001).

Analysis of pooled events from PLAC I, the Pravastatin, Lipids and Atherosclerosis in the Carotids Study (PLAC II)[5], REGRESS, and the Kuopio Atherosclerosis Prevention Study (KAPS)[7] (combined N=1891) showed that treatment with pravastatin was associated with a statistically significant reduction in the composite event rate of fatal and non-fatal myocardial infarction (46 events or 6.4% for placebo versus 21 events or 2.4% for pravastatin, p=0.001). The predominant effect of pravastatin was to reduce the rate of non-fatal myocardial infarction.

Primary Hypercholesterolemia (Fredrickson Type IIa and IIb)

PRAVACHOL (pravastatin sodium) is highly effective in reducing Total-C, LDL-C and Triglycerides (TG) in patients with heterozygous familial, presumed familial combined and non-familial (non-FH) forms of primary hypercholesterolemia, and mixed dyslipidemia. A therapeutic response is seen within 1 week, and the maximum response usually is achieved within 4 weeks. This response is maintained during extended periods of therapy. In addition, PRAVACHOL is effective in reducing the risk of acute coronary events in hypercholesterolemic patients with and without previous myocardial infarction.

A single daily dose is as effective as the same total daily dose given twice a day. In multicenter, double-blind, placebo-controlled studies of patients with primary hypercholesterolemia, treatment with pravastatin in daily doses ranging from 10 mg to 40 mg consistently and significantly decreased Total-C, LDL-C, TG, and Total-C/HDL-C and LDL-C/HDL-C ratios (see **Table 3**).

In a pooled analysis of two multicenter, double-blind, placebo-controlled studies of patients with primary hypercholesterolemia, treatment with pravastatin at a daily dose of 80 mg (N=277) significantly decreased Total-C, LDL-C, and TG. The 25th and 75th percentile changes from baseline in LDL-C for pravastatin 80 mg were -43% and -30%. The efficacy results of the individual studies were consistent with the pooled data (see **Table 3**).

Treatment with PRAVACHOL modestly decreased VLDL-C and PRAVACHOL across all doses produced variable increases in HDL-C (see **Table 3**).

Table 3: Primary Hypercholesterolemia Studies: Dose Response of PRAVACHOL Once Daily Administration

Dose	Total-C	LDL-C	HDL-C	TG
Mean Percent Changes From Baseline After 8 Weeks*				
Placebo (N=36)	-3%	-4%	+1%	-4%
10 mg (N=18)	-16%	-22%	+7%	-15%
20 mg (N=19)	-24%	-32%	+2%	-11%
40 mg (N=18)	-25%	-34%	+12%	-24%
Mean Percent Changes From Baseline After 6 Weeks**				
Placebo (N=162)	0%	-1%	-1%	+1%
80 mg (N=277)	-27%	-37%	+3%	-19%

*a multicenter, double-blind, placebo-controlled study
**pooled analysis of 2 multicenter, double-blind, placebo-controlled studies

In another clinical trial, patients treated with pravastatin in combination with cholestyramine (70% of patients were taking cholestyramine 20 or 24 g per day) had reductions equal to or greater than 50% in LDL-C. Furthermore, pravastatin attenuated cholestyramine-induced increases in TG levels (which are themselves of uncertain clinical significance).

Hypertriglyceridemia (Fredrickson Type IV)

The response to pravastatin in patients with Type IV hyperlipidemia (baseline TG >200 mg/dL and LDL-C <160 mg/dL) was evaluated in a subset of 429 patients from the Cholesterol and Recurrent Events (CARE) study. For pravastatin-treated subjects, the median (min, max) baseline triglyceride level was 246.0 (200.5, 349.5) mg/dL (see Table 4).

Table 4: Patients With Fredrickson Type IV Hyperlipidemia Median (25th, 75th percentile) Percent Change From Baseline

	Pravastatin 40 mg (N=429)	Placebo (N=430)
Triglycerides	-21.1 (-34.8, 1.3)	-6.3 (-23.1, 18.3)
Total-C	-22.1 (-27.1, -14.8)	0.2 (-6.9, 6.8)
LDL-C	-31.7 (-39.6, -21.5)	0.7 (-9.0, 10.0)
HDL-C	7.4 (-1.2, 17.7)	2.8 (-5.7, 11.7)
Non-HDL-C	-27.2 (-34.0, -18.5)	-0.8 (-8.2, 7.0)

Dysbetalipoproteinemia (Fredrickson Type III)

The response to pravastatin in two double-blind crossover studies of 46 patients with genotype E2/E2 and Fredrickson Type III dysbetalipoproteinemia is shown in **Table 5**.

Table 2: CARE – Primary and Secondary Endpoints

Event	Number (%) of Subjects: Pravastatin 40 mg (N=2081)	Placebo (N=2078)	Risk Reduction	P-value
Primary Endpoint				
CHD mortality or non-fatal MI*	212 (10.2)	274 (13.2)	24%	0.003
Secondary Endpoints				
Myocardial revascularization procedures (CABG or PTCA)	294 (14.1)	391 (18.8)	27%	<0.001
Stroke or TIA	93 (4.5)	124 (6.0)	26%	0.029

* The risk reduction due to treatment with PRAVACHOL was consistent in both sexes.

Table 6: Lipid-Lowering Effects of Pravastatin in Pediatric Patients with Heterozygous Familial Hypercholesterolemia: Least-Squares Mean Percent Change from Baseline at Month 24 (Last Observation Carried Forward: Intent-to-Treat)*

	Pravastatin 20 mg (Aged 8–13 years) N=65	Pravastatin 40 mg (Aged 14–18 years) N=41	Combined Pravastatin (Aged 8–18 years) N=106	Combined Placebo (Aged 8–18 years) N=108	95% CI of the Difference Between Combined Pravastatin and Placebo
LDL-C	−26.04**	−21.07**	−24.07**	−1.52	(−26.74, −18.86)
TC	−20.75**	−13.08**	−17.72**	−0.65	(−20.40, −13.83)
HDL-C	1.04	13.71	5.97	3.13	(−1.71, 7.43)
TG	−9.58	−0.30	−5.88	-3.27	(-13.95, 10.01)
ApoB (N)	-23.16** (61)	-18.08** (39)	-21.11** (100)	-0.97 (106)	(-24.29, -16.18)

*The above least-squares mean values were calculated based on log-transformed lipid values.
**Significant at p≤0.0001 when compared with placebo.

Table 5: Patients With Fredrickson Type III Dysbetalipoproteinemia Median (min, max) Percent Change From Baseline

	Median (min, max) at Baseline (mg/dL)	Median % Change (min, max) Pravastatin 40 mg (N=20)
Study 1		
Total-C	386.5 (245.0, 672.0)	-32.7 (-58.5, 4.6)
Triglycerides	443.0 (275.0, 1299.0)	-23.7 (-68.5, 44.7)
VLDL-C*	206.5 (110.0, 379.0)	-43.8 (-73.1, -14.3)
LDL-C*	117.5 (80.0, 170.0)	-40.8 (-63.7, 4.6)
HDL-C	30.0 (18.0, 88.0)	6.4 (-45.0, 105.6)
Non-HDL-C	344.5 (215.0, 646.0)	-36.7 (-66.3, 5.8)
*N=14		

	Median (min, max) at Baseline (mg/dL)	Median % Change (min, max) Pravastatin 40 mg (N=26)
Study 2		
Total-C	340.3 (230.1, 448.6)	-31.4 (-54.5, -13.0)
Triglycerides	343.2 (212.6, 845.9)	-11.9 (-56.5, 44.8)
VLDL-C	145.0 (71.5, 309.4)	-35.7 (-74.7, 19.1)
LDL-C	128.6 (63.8, 177.9)	-30.3 (-52.2, 13.5)
HDL-C	38.7 (27.1, 58.0)	5.0 (-17.7, 66.7)
Non-HDL-C	295.8 (195.3, 421.5)	-35.5 (-81.0, -13.5)

Pediatric Clinical Study

A double-blind placebo-controlled study in 214 patients (100 boys and 114 girls) with heterozygous familial hypercholesterolemia (HeFH), aged 8-18 years was conducted for two (2) years. The children (aged 8-13 years) were randomized to placebo (n=63) or 20 mg of pravastatin daily (n=65) and the adolescents (aged 14-18 years) were randomized to placebo (n=45) or 40 mg of pravastatin daily (n=41). Inclusion in the study required LDL-C level >95th percentile for age and sex and one parent with either a clinical or molecular diagnosis of familial hypercholesterolemia. The mean baseline LDL-C value was 239 mg/dL and 237 mg/dL in the pravastatin (range: 151-405 mg/dL) and placebo (range: 154-375 mg/dL) groups, respectively.

Pravastatin significantly decreased plasma levels of LDL-C, Total-C, and apolipoprotein B in both children and adolescents (see **Table 6**). The effect of pravastatin treatment in the two age groups was similar.

[See table 6 above]

The mean achieved LDL-C was 186 mg/dL (range: 67–363 mg/dL) in the pravastatin group compared to 236 mg/dL (range: 105–438 mg/dL) in the placebo group.

The safety and efficacy of pravastatin doses above 40 mg daily have not been studied in children. The long-term efficacy of pravastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

INDICATIONS AND USAGE

Therapy with PRAVACHOL (pravastatin sodium) should be considered in those individuals at increased risk for atherosclerosis-related clinical events as a function of cholesterol level, the presence or absence of coronary heart disease, and other risk factors.

Primary Prevention of Coronary Events

In hypercholesterolemic patients without clinically evident coronary heart disease, PRAVACHOL (pravastatin sodium) is indicated to:

- — Reduce the risk of myocardial infarction
- — Reduce the risk of undergoing myocardial revascularization procedures
- — Reduce the risk of cardiovascular mortality with no increase in death from non-cardiovascular causes.

Secondary Prevention of Cardiovascular Events

In patients with clinically evident coronary heart disease, PRAVACHOL is indicated to:

- — Reduce the risk of total mortality by reducing coronary death
- — Reduce the risk of myocardial infarction
- — Reduce the risk of undergoing myocardial revascularization procedures
- — Reduce the risk of stroke and stroke/transient ischemic attack (TIA)
- — Slow the progression of coronary atherosclerosis.

Hyperlipidemia

PRAVACHOL is indicated as an adjunct to diet to reduce elevated Total-C, LDL-C, Apo B, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia (Fredrickson Type IIa and IIb).[8]

PRAVACHOL is indicated as adjunctive therapy to diet for the treatment of patients with elevated serum triglyceride levels (Fredrickson Type IV).

PRAVACHOL is indicated for the treatment of patients with primary dysbetalipoproteinemia (Fredrickson Type III) who do not respond adequately to diet.

PRAVACHOL is indicated as an adjunct to diet and lifestyle modification for treatment of HeFH in children and adolescent patients ages 8 years and older if after an adequate trial of diet the following findings are present.

1. LDL-C remains ≥190 mg/dL or
2. LDL-C remains ≥160 mg/dL and;
   - — there is a positive family history of premature cardiovascular disease or
   - — two or more other CVD risk factors are present in the patient.

Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol when the response to diet and other nonpharmacological measures alone has been inadequate (see NCEP Guidelines below).

Prior to initiating therapy with pravastatin, secondary causes for hypercholesterolemia (e.g., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism) should be excluded, and a lipid profile performed to measure Total-C, HDL-C, and TG. For patients with triglycerides (TG) <400 mg/dL (<4.5 mmol/L), LDL-C can be estimated using the following equation:

$$\text{LDL-C} = \text{Total-C} - \text{HDL-C} - \tfrac{1}{5}\,\text{TG}$$

For TG levels >400 mg/dL (>4.5 mmol/L), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation. In many hypertriglyceridemic patients, LDL-C may be low or normal despite elevated Total-C. In such cases, HMG-CoA reductase inhibitors are not indicated.

Continued on next page

Pravachol—Cont.

Lipid determinations should be performed at intervals of no less than four weeks and dosage adjusted according to the patient's response to therapy.

The National Cholesterol Education Program's Treatment Guidelines are summarized below:

[See table 7 below]

After the LDL-C goal has been achieved, if the TG is still ≥200 mg/dL, non-HDL-C (Total-C minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk category.

At the time of hospitalization for an acute coronary event, consideration can be given to initiating drug therapy at discharge if the LDL-C is ≥130 mg/dL (see NCEP Treatment Guidelines, above).

Since the goal of treatment is to lower LDL-C, the NCEP recommends that LDL-C levels be used to initiate and assess treatment response. Only if LDL-C levels are not available, should the Total-C be used to monitor therapy.

As with other lipid-lowering therapy, PRAVACHOL (pravastatin sodium) is not indicated when hypercholesterolemia is due to hyperalphalipoproteinemia (elevated HDL-C).

The NCEP classification of cholesterol levels in pediatric patients with a familial history of hypercholesterolemia or premature cardiovascular disease is summarized below:

Category	Total-C (mg/dL)	LDL-C (mg/dL)
Acceptable	<170	<110
Borderline	170-199	110-129
High	≥200	≥130

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained, persistent elevations of serum transaminases (see **WARNINGS**).

Pregnancy and Lactation. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they are contraindicated during pregnancy and in nursing mothers. **Pravastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued immediately and the patient apprised of the potential hazard to the fetus (see **PRECAUTIONS: Pregnancy**).

WARNINGS

Liver Enzymes

HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. In three long-term (4.8-5.9 years), placebo-controlled clinical trials (WOS, LIPID, CARE; see **CLINICAL PHARMACOLOGY: Clinical Studies**), 19,592 subjects (19,768 randomized), were exposed to pravastatin or placebo. In an analysis of serum transaminase values (ALT, AST), incidences of marked abnormalities were compared between the pravastatin and placebo treatment groups; a marked abnormality was defined as a post-treatment test value greater than three times the upper limit of normal for subjects with pretreatment values less than or equal to the upper limit of normal, or four times the pretreatment value for subjects with pretreatment values greater than the upper limit of normal but less than 1.5 times the upper limit of normal. Marked abnormalities of ALT or AST occurred with similar low frequency (≤1.2%) in both treatment groups. Overall, clinical trial experience showed that liver function test abnormalities observed during pravastatin therapy were usually asymptomatic, not associated with cholestasis, and did not appear to be related to treatment duration.

It is recommended that liver function tests be performed prior to the initiation of therapy, prior to the elevation of the dose, and when otherwise clinically indicated.

Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of pravastatin (see **CONTRAINDICATIONS**). Caution should be exercised when pravastatin is administered to patients who have a recent history of liver disease, have signs that may suggest liver disease (e.g., unexplained aminotransferase elevations, jaundice), or are heavy users of alcohol (see **CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism**). Such patients should be closely monitored, started at the lower end of the recommended dosing range, and titrated to the desired therapeutic effect.

Patients who develop increased transaminase levels or signs and symptoms of liver disease should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return to normal. Should an increase in AST or ALT of three times the upper limit of normal or greater persist, withdrawal of pravastatin therapy is recommended.

Skeletal Muscle

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with pravastatin and other drugs in this class. Uncomplicated myalgia has also been reported in pravastatin-treated patients (see **ADVERSE REACTIONS**). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal, was rare (<0.1%) in pravastatin clinical trials. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.**

The risk of myopathy during treatment with another HMG-CoA reductase inhibitor is increased with concurrent therapy with either erythromycin, cyclosporine, niacin, or fibrates. However, neither myopathy nor significant increases in CPK levels have been observed in three reports involving a total of 100 post-transplant patients (24 renal and 76 cardiac) treated for up to two years concurrently with pravastatin 10-40 mg and cyclosporine. Some of these patients also received other concomitant immunosuppressive therapies. Further, in clinical trials involving small numbers of patients who were treated concurrently with pravastatin and niacin, there were no reports of myopathy. Also, myopathy was not reported in a trial of combination pravastatin (40 mg/day) and gemfibrozil (1200 mg/day), although 4 of 75 patients on the combination showed marked CPK elevations versus one of 73 patients receiving placebo. There was a trend toward more frequent CPK elevations and patient withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy (see **PRECAUTIONS: Drug Interactions**). **The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination.**

PRECAUTIONS

General

PRAVACHOL (pravastatin sodium) may elevate creatine phosphokinase and transaminase levels (see **ADVERSE REACTIONS**). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

Homozygous Familial Hypercholesterolemia

Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors.

Renal Insufficiency

A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3α-hydroxy isomeric metabolite (SQ 31,906). A small increase was seen in mean AUC values and half-life ($t_{1/2}$) for the inactive enzymatic ring hydroxylation metabolite (SQ 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored.

Information for Patients

Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever (see **WARNINGS: Skeletal Muscle**).

Drug Interactions

Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin: See **WARNINGS: Skeletal Muscle.**

Cytochrome P450 3A4 Inhibitors: *In vitro* and *in vivo* data indicate that pravastatin is not metabolized by cytochrome P450 3A4 to a clinically significant extent. This has been shown in studies with known cytochrome P450 3A4 inhibitors (see diltiazem and itraconazole below). Other examples of cytochrome P450 3A4 inhibitors include ketoconazole, mibefradil, and erythromycin.

Diltiazem: Steady-state levels of diltiazem (a known, weak inhibitor of P450 3A4) had no effect on the pharmacokinetics of pravastatin. In this study, the AUC and C_{max} of another HMG-CoA reductase inhibitor which is known to be metabolized by cytochrome P450 3A4 increased by factors of 3.6 and 4.3, respectively.

Itraconazole: The mean AUC and C_{max} for pravastatin were increased by factors of 1.7 and 2.5, respectively, when given with itraconazole (a potent P450 3A4 inhibitor which also inhibits p-glycoprotein transport) as compared to placebo. The mean $t_{1/2}$ was not affected by itraconazole, suggesting that the relatively small increases in C_{max} and AUC were due solely to increased bioavailability rather than a decrease in clearance, consistent with inhibition of p-glycoprotein transport by itraconazole. This drug transport system is thought to affect bioavailability and excretion of HMG-CoA reductase inhibitors, including pravastatin. The AUC and C_{max} of another HMG-CoA reductase inhibitor which is known to be metabolized by cytochrome P450 3A4 increased by factors of 19 and 17, respectively, when given with itraconazole.

Antipyrine: Since concomitant administration of pravastatin had no effect on the clearance of antipyrine, interactions with other drugs metabolized via the same hepatic cytochrome isozymes are not expected.

Cholestyramine/Colestipol: Concomitant administration resulted in an approximately 40 to 50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours after cholestyramine or 1 hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect. (See **DOSAGE AND ADMINISTRATION: Concomitant Therapy.**)

Warfarin: Concomitant administration of 40 mg pravastatin had no clinically significant effect on prothrombin time when administered in a study to normal elderly subjects who were stabilized on warfarin.

Cimetidine: The AUC_{0-12hr} for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUC's for pravastatin when given with cimetidine compared to when administered with antacid.

Digoxin: In a crossover trial involving 18 healthy male subjects given 20 mg pravastatin and 0.2 mg digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SQ 31,906 and SQ 31,945 was not altered.

Cyclosporine: Some investigators have measured cyclosporine levels in patients on pravastatin (up to 20 mg), and to date, these results indicate no clinically meaningful el-

Table 7: NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Levels at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD[a] or CHD Risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100-129: drug optional)[b]
2+ Risk factors (10-year risk ≤20%)	<130	≥130	10-year risk 10%-20%: ≥130
			10-year risk <10%: ≥160
0-1 Risk factor[c]	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

[a] CHD, coronary heart disease.

[b] Some authorities recommend the use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgement also may call for deferring drug therapy in this subcategory.

[c] Almost all people with 0-1 risk factor have 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

evations in cyclos
pravastatin levels
transplant patient
Gemfibrozil: In a
unteers given conc
gemfibrozil, there
cretion and prote
there was a signifi
the pravastatin m
with pravastatin
mended. (See **WA**
In interaction stud
PRAVACHOL), *ci*
statistically signi
seen when PR
administered.
Endocrine Functic
HMG-CoA reduct
synthesis and lov
such, might theo
hormone producti
tin in males and
tent with regard
roid hormone le
testosterone resp
significantly redu
with 40 mg of pr
tients showing a
man chorionic go
nificantly after
HMG-CoA reduct
tility have not b
tients. The effec
gonadal axis in
Patients treated
dence of endocri
priately. Caution
reductase inhibit
levels is adminis
(e.g., ketoconazo
minish the level
In a placebo-con
HeFH, of which
in the children a
aged 14-18 year
differences seen
cortisol, DHEAS
terone (boys)] re
differences seen
volume changes
CNS Toxicity
CNS vascular le
rhage and eden
vascular spaces
at a dose of 25
served at app
80 mg/day, bas
have been obse
A chemically sir
degeneration (V
bers) in clinica
starting at 60 n
drug levels abo
in humans tak
sured by total
also produced
tion and retina
for 14 weeks a
mean plasma
60 mg/kg/day
Carcinogenesis
In a 2-year stu
or 100 mg/kg b
of hepatocellu
($p<0.01$). The
mately 12 tim
body surface a
human dose, b
In a 2-year stu
500 mg/kg/day
cellular carcir
500 mg/kg/da
in females we
were observe
and 23 times
based on AUC
up to 100 m
mately 2 tim
there were nc
No evidence
without rat-li
ies: microbial
monella typh
tion assay i
chromosomal
conversion a
tion, there w
inant lethal
In a study ir
astatin did
general repr
another HM
fertility in m

evations in cyclosporine levels. In one single-dose study, pravastatin levels were found to be increased in cardiac transplant patients receiving cyclosporine.

Gemfibrozil: In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, C_{max}, and T_{max} for the pravastatin metabolite SQ 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended. (See **WARNINGS: Skeletal Muscle.**)

In interaction studies with *aspirin, antacids* (1 hour prior to PRAVACHOL), *cimetidine, nicotinic acid,* or *probucol,* no statistically significant differences in bioavailability were seen when PRAVACHOL (pravastatin sodium) was administered.

Endocrine Function

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced ($p<0.004$) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a ≥50% rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of HMG-CoA reductase inhibitors on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in pre-menopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may diminish the levels or activity of steroid hormones.

In a placebo-controlled study of 214 pediatric patients with HeFH, of which 106 were treated with pravastatin (20 mg in the children aged 8-13 years and 40 mg in the adolescents aged 14-18 years) for two years, there were no detectable differences seen in any of the endocrine parameters [ACTH, cortisol, DHEAS, FSH, LH, TSH, estradiol (girls) or testosterone (boys)] relative to placebo. There were no detectable differences seen in height and weight changes, testicular volume changes, or Tanner score relative to placebo.

CNS Toxicity

CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day. These effects in dogs were observed at approximately 59 times the human dose of 80 mg/day, based on AUC. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg/day dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose ($p<0.01$). These effects in rats were observed at approximately 12 times the human dose (HD) of 80 mg, based on body surface area mg/m^2 and at approximately 4 times the human dose, based on AUC.

In a 2-year study in mice fed pravastatin at doses of 250 and 500 mg/kg/day, there was an increased incidence of hepatocellular carcinomas in males and females at both 250 and 500 mg/kg/day ($p<0.0001$). At these doses, lung adenomas in females were increased ($p=0.013$). These effects in mice were observed at approximately 15 times (250 mg/kg/day) and 23 times (500 mg/kg/day) the human dose of 80 mg, based on AUC. In another 2-year study in mice with doses up to 100 mg/kg/day (producing drug exposures approximately 2 times the human dose of 80 mg, based on AUC), there were no drug-induced tumors.

No evidence of mutagenicity was observed *in vitro*, with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests, using mutant strains of *Salmonella typhimurium* or *Escherichia coli*; a forward mutation assay in L5178Y TK +/- mouse lymphoma cells; a chromosomal aberration test in hamster cells; and a gene conversion assay using *Saccharomyces cerevisiae*. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a study in rats, with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance. However, in a study with another HMG-CoA reductase inhibitor, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. Although not seen with pravastatin, two similar drugs in this class caused drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation in dogs. The clinical significance of these findings is unclear.

Table 8: Adverse Events in >2 Percent of Patients Treated with Pravastatin 10-40 mg in Short-Term Placebo-Controlled Trials

	All Events		Events Attributed to Study Drug	
Body System/Event	**Pravastatin (N=900) % of patients**	**Placebo (N=411) % of patients**	**Pravastatin (N=900) % of patients**	**Placebo (N=411) % of patients**
Cardiovascular				
Cardiac Chest Pain	4.0	3.4	0.1	0.0
Dermatologic				
Rash	4.0*	1.1	1.3	0.9
Gastrointestinal				
Nausea/Vomiting	7.3	7.1	2.9	3.4
Diarrhea	6.2	5.6	2.0	1.9
Abdominal Pain	5.4	6.9	2.0	3.9
Constipation	4.0	7.1	2.4	5.1
Flatulence	3.3	3.6	2.7	3.4
Heartburn	2.9	1.9	2.0	0.7
General				
Fatigue	3.8	3.4	1.9	1.0
Chest Pain	3.7	1.9	0.3	0.2
Influenza	2.4*	0.7	0.0	0.0
Musculoskeletal				
Localized Pain	10.0	9.0	1.4	1.5
Myalgia	2.7	1.0	0.6	0.0
Nervous System				
Headache	6.2	3.9	1.7*	0.2
Dizziness	3.3	3.2	1.0	0.5
Renal / Genitourinary				
Urinary Abnormality	2.4	2.9	0.7	1.2
Respiratory				
Common Cold	7.0	6.3	0.0	0.0
Rhinitis	4.0	4.1	0.1	0.0
Cough	2.6	1.7	0.1	0.0

*Statistically significantly different from placebo.

Pregnancy

Pregnancy Category X.

See **CONTRAINDICATIONS.**

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg daily or in rabbits at doses of up to 50 mg/kg daily. These doses resulted in 10X (rabbit) or 120X (rat) the human exposure based on surface area (mg/meter^2). Rare reports of congenital anomalies have been received following intrauterine exposure to other HMG-CoA reductase inhibitors. In a review[9] of approximately 100 prospectively followed pregnancies in women exposed to simvastatin or lovastatin, the incidences of congenital anomalies, spontaneous abortions and fetal deaths/stillbirths did not exceed what would be expected in the general population. The number of cases is adequate only to exclude a three-to-four-fold increase in congenital anomalies over the background incidence. In 89% of the prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified. As safety in pregnant women has not been established and there is no apparent benefit to therapy with PRAVACHOL (pravastatin sodium) during pregnancy (see **CONTRAINDICATIONS**), treatment should be immediately discontinued as soon as pregnancy is recognized. PRAVACHOL (pravastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards.

Nursing Mothers

A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking PRAVACHOL should not nurse (see **CONTRAINDICATIONS**).

Pediatric Use

The safety and effectiveness of PRAVACHOL in children and adolescents from 8-18 years of age have been evaluated in a placebo-controlled study of two years duration. Patients treated with pravastatin had an adverse experience profile generally similar to that of patients treated with placebo with influenza and headache commonly reported in both treatment groups. (See **ADVERSE REACTIONS: Pediatric Patients.**) **Doses greater than 40 mg have not been studied in this population.** Children and adolescent females of childbearing potential should be counseled on appropriate contraceptive methods while on pravastatin therapy (see **CONTRAINDICATIONS** and **PRECAUTIONS: Pregnancy**). For dosing information see **DOSAGE AND ADMINISTRATION: Adult Patients** and **Pediatric Patients.**

Double-blind, placebo-controlled pravastatin studies in children less than 8 years of age have not been conducted.

Geriatric Use

Two secondary prevention trials with pravastatin (CARE and LIPID) included a total of 6,593 subjects treated with pravastatin 40 mg for periods ranging up to 6 years. Across these two studies, 36.1% of pravastatin subjects were aged 65 and older and 0.8% were aged 75 and older. The beneficial effect of pravastatin in elderly subjects in reducing cardiovascular events and in modifying lipid profiles was similar to that seen in younger subjects. The adverse event profile in the elderly was similar to that in the overall population. Other reported clinical experience has not identified differences in responses to pravastatin between elderly and younger patients.

Mean pravastatin AUCs are slightly (25-50%) higher in elderly subjects than in healthy young subjects, but mean C_{max}, T_{max} and $t_{1/2}$ values are similar in both age groups and substantial accumulation of pravastatin would not be expected in the elderly (see **CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism**).

ADVERSE REACTIONS

Pravastatin is generally well tolerated; adverse reactions have usually been mild and transient. In 4-month long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy; this difference was not statistically significant. (See also **PRECAUTIONS: Geriatric Use** section).

Adverse Clinical Events

Short-Term Controlled Trials

All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in placebo-controlled trials of up to four months duration are identified in **Table 8**; also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug:

[See table 8 above]

The safety and tolerability of PRAVACHOL (pravastatin sodium) at a dose of 80 mg in two controlled trials with a mean exposure of 8.6 months was similar to that of PRAVACHOL at lower doses except that 4 out of 464 patients taking 80 mg of pravastatin had a single elevation of CK >10× ULN compared to 0 out of 115 patients taking 40 mg of pravastatin.

Long-Term Controlled Morbidity and Mortality Trials

Adverse event data were pooled from seven double-blind, placebo-controlled trials (West of Scotland Coronary Prevention study [WOS]; Cholesterol and Recurrent Events study [CARE]; Long-term Intervention with Pravastatin in Ischemic Disease study [LIPID]; Pravastatin Limitation of Atherosclerosis in the Coronary Arteries study [PLAC I]; Pravastatin, Lipids and Atherosclerosis in the Carotids study [PLAC II]; Regression Growth Evaluation Statin Study [REGRESS]; and Kuopio Atherosclerosis Prevention Study [KAPS]) involving a total of 10,764 patients treated with pravastatin 40 mg and 10,719 patients treated with placebo. The safety and tolerability profile in the pravastatin group was comparable to that of the placebo group. Patients were exposed to pravastatin for a mean of 4.0 to 5.1 years in WOS, CARE, and LIPID and 1.9 to 2.9 years in PLAC I, PLAC II, KAPS, and REGRESS. In these long-term trials, the most common reasons for discontinuation were mild, non-specific gastrointestinal complaints. Collectively, these seven trials represent 47,613 patient-years of exposure to pravastatin. Events believed to be of probable, possible, or uncertain relationship to study drug, occurring in at least 1% of patients treated with pravastatin in these studies are identified in **Table 9.**

Continued on next page